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REGIONAL CEREBRAL BLOOD FLOW FOLLOWING INDUCED SUBARACHNOID HEMORRHAGE IN MONKEYS

by

© Guy Roger West

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

Department of Medicine

EDMONTON, ALBERTA

FALL, 1970

Thesis
1976 F
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UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Regional Cerebral Blood Flow Following Induced Subarachnoid Hemorrhage in Monkeys" submitted by Guy Roger West in partial fulfilment of the requirements for the degree of Master of Science.

ABSTRACT

The effect of artificially induced subarachnoid hemorrhage upon cerebral blood flow in rhesus monkeys has been studied.

Subarachnoid hemorrhage was simulated by injecting fresh autogenous blood through a needle positioned in the chiasmatic cistern. Cerebral blood flow was determined by the method of Ingvar and Lassen whereby the clearance of ^{133}Xe from the brain was monitored with a single scintillation detector directed over the parietal area.

For a period exceeding one hour cerebral blood flow following the induced subarachnoid hemorrhage was not found to differ significantly from prehemorrhage values. In most of the animals studied, after this post hemorrhage interval, the cerebral blood flow was found to gradually decrease until the termination of the experiment.

Other physiological parameters monitored throughout the experiment included EEG, ECG, B.P., and CSF pressure.

A good correlation between cerebral blood flow and the frequency content of the EEG was found.

The conclusion,resulting from this investigation, was that the reduction in cerebral blood flow following subarachnoid hemorrhage is related to factors other than the vasoconstriction caused by the contact of cerebral blood vessels with fresh autogenous blood.

ACKNOWLEDGEMENTS

Dr. T. R. Overton, my supervisor, for his enduring tolerance, encouragement and guidance.

Dr. J. R. MacIntyre, for his anesthetic assistance and his experience in cerebral vascular physiology.

Michael Marriott, for his generous contributions to the computer analysis and programming.

Joan Wettlaufer, for her willing and untiring technical assistance during the experimental procedures and her assistance in the preparation of this thesis.

Dr. B. K. Weir, for his advice, suggestions and support of the project.

Dr. J. D. R. Miller, for his assistance in x-ray interpretation.

Dr. B. Mielke, for his assistance in pathological studies.

Dr. D. Secord and his staff, for the care and assistance in handling the animals.

Dr. G. Moncton, for his support.

Dr. C. M. Couves, for the extended loan of Beckman Dynagraph and Tape Recording instrumentation.

Trudy Commandeur, for the typing of this thesis.

This work was supported in part by Medical Research Council grants awarded to Dr. B. K. Weir (MA 4054) and Dr. T. R. Overton (MA 3352) and also a Medical Research Fund grant made to Dr. J. D. R. Miller (MR3-363). Extensive support, in the form of laboratory space, technical assistance and instrumentation, was provided by the Division of Biomedical Engineering, Faculty of Medicine.

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CHAPTER I

INTRODUCTION

Subarachnoid hemorrhage from rupture of a cerebral aneurysm is a relatively uncommon form of cerebrovascular disease; however, the mortality and morbidity in this condition is high. Refinement in surgical techniques has introduced a positive approach in the treatment of cerebral aneurysms, resulting in a decrease in mortality and morbidity.

The greatest risk to the patient after rupture of a cerebral aneurysm is a second bleed. The critical time for rebleeding is in the first month following the initial rupture and is associated with a very marked increase in the mortality and morbidity.

The objective in treatment is directed at prevention of a second hemorrhage. Ideally, surgery is performed early providing the patients condition permits. Factors leading to delay in surgical treatment are:

i) an altered state of consciousness,

ii) the radiological appearance of vasospasm on radio-contrast studies of the cerebral circulation.

Both factors are associated with a high surgical failure in terms of morbidity and mortality. It is therefore evident that a thorough understanding of the pathophysiology of these phenomena is required.

James (29) has shown a significant correlation between cerebral blood flow and the state of consciousness in patients with a subarachnoid hemorrhage from a ruptured aneurysm; he concluded the decrease in flow was due to vasospasm.

Zingesser (73) found no correlation between cerebral blood flow and vasospasm.

On some occasions patients, with subarachnoid hemorrhage resulting from ruptured cerebral aneurysms and demonstrating vasospasm of the aneurysmal vessel, will have minimal or no alteration in consciousness. One must assume cerebral blood flow is adequate for normal cerebral function in these cases.

The natural question arises - is the vasospasm in the aneurysmal cerebral vessel visualized during radio-contrast studies, following rupture of the aneurysm, significant in terms of affecting cerebral blood flow?

The general consensus of opinion, arising mainly from clinical studies (1,14,65) is that vasospasm is highly significant and the majority of surgeons agree that presence of vasospasm is a contraindication for operative interference in subarachnoid hemorrhage. Proof that vasospasm is critical in terms of a reduction of cerebral blood has not yet been shown.

It is evident that further studies on cerebral blood flow in subarachnoid hemorrhage are required. If vasospasm is significant one could readily demonstrate this by showing a decrease in cerebral blood flow in the presence of vasospasm before cerebral edema was manifest.

This study was undertaken to determine the cerebral blood flow following artificially induced subarachnoid hemorrhage. In a previous study (12) it was shown that significant vasospasm of all major cerebral blood vessels occurred in a high proportion of animals when fresh autogenous blood was introduced into the subarachnoid space at the base of the brain such that the major vessels were bathed in blood. The vasospasm was diffuse and reached a maximum within twenty minutes.

Vasospasm is not the only pathophysiological mechanism operating following subarachnoid hemorrhage. A metabollic acidosis of cerebrospinal fluid is known to occur (16) and an increase in cerebral blood flow would be anticipated following the hemorrhage secondary to dilitation of cerebral arterioles.

Two opposing effects are therefore evident. If vasospasm is significant a decrease in cerebral blood flow should be demonstrable even though a posthypoxic vasodilitation of arterioles was present.

Kety and Schmidt (37) developed a method of measuring cerebral blood flow utilizing a freely diffusible inert gas. The theory is based on the Fick principle, the value obtained being an estimate of cerebral blood flow per unit weight of tissue. Through refinements in the technique, and later modifications including use of radioactive indicators, a method was developed by Ingvar and Lassen (28) whereby the washout of a freely diffusible inert radioactive indicator (^{133}Xe) from brain is measured with external detectors. Various methods of calculation of mean cerebral blood flow are available each having specific limitations. An index of cortical blood flow can be achieved from compartmental analysis of the semilogarithmic replot of the count rate versus time. This method of determining cerebral blood flow is proven and results are reproducible.

Using the method of Ingvar and Lassen to measure cerebral blood flow it was proposed to study the effect of artificially induced subarachnoid hemorrhage on cerebral blood flow in monkeys. A method of inducing subarachnoid hemorrhage which has been described previously (12), is used in this study. As the vasospasm induced by the fresh autogenous blood is diffuse one is justified in using a single, well collimated probe for detecting the washout of the radioactive indicator for

calculation of an index of cerebral blood flow. The assumption was made that study of a single area over the parietal area would be an adequate monitor of changes occurring throughout the brain providing no gross anatomical lesion was evident at the end of the study.

As cerebral resistance is a basic property of arterioles, capillaries and viscosity, a change in calibre of a large cerebral artery would not be expected to cause a major alteration in capillary blood flow (effective tissue flow). Cerebral edema found in the majority of patients dying as a result of hemorrhage increases cerebrovascular resistance probably at the capillary level.

The hypothesis set forth was that cerebral blood flow would not be significantly reduced by a decrease in the calibre of major cerebral vessels induced by introducing fresh autogenous into the subarachnoid space such that these vessels would be bathed in blood. Furthermore, a hypoxic event occurs during the introduction of the blood and, depending upon the degree of metabolic acidosis resulting from the hypoxia, the cerebral blood flow would be expected to increase or remain the same. Cerebral edema if present would not be evident immediately and would be expected to effect a decrease in cerebral blood flow later than that occurring due to vasospasm.

CHAPTER II

REVIEW OF LITERATURE

2.1 Cerebral Blood Flow in Subarachnoid Hemorrhage

2.1.1 Evidence of Vasospasm

Ecker and Riemenschneider (11) showed by radiocontrast study of the cerebral circulation that narrowing of arteries occurred following rupture of a congenital cerebral aneurysm. This has been confirmed by others (14, 31, 55,65). Since the demonstration of vasospasm in subarachnoid hemorrhage many clinical experimental investigations have failed to unveil the etiology, pathophysiology,or treatment of this phenomenon. Implicated, but not proven, as the etiological factor are neurogenic, mechanical, a vaso-active factor in blood, and edema of the vessel wall (9). The current feeling is that a combination of mechanical factors and a vaso-active factor in blood (33) is responsible for the prolonged vasospasm that occurs following rupture of a cerebral aneurysm.

Brawley (4), Landau (40), Simeone (62), and Symon (66), have produced prolonged vasospasm by avulsion of a vessel with a previously applied suture or by puncture of a vessel with a fine needle. Fresh blood in contact with cerebral vessels at the base of the brain will cause vasospasm as previously demonstrated by Chow (6), Echlin (10), Landau (40), Kapp (34), and Erasmo (12). The spasm is local if the blood remains local (10), but is diffuse if the blood is allowed to spread over the surface of the cortex.

The duration of spasm induced by fresh blood is short, probably not exceeding one hour. Constriction of the basilar and vertebral arteries to 60% of the control size has been shown to occur with application of blood (10).

The significance of vasospasm has never been confirmed. Clinical reports conclude that vasospasm is responsible for increased morbidity and mortality in patients demonstrating this phenomenon (1, 2, 26, 65).

Symon (66) measured cerebral blood flow by thermal diffusion techniques in the territory of the middle cerebral artery after causing spasm by mechanical stimulation. He found a marked decrease in the temperature of the tissue distal to the spasm. However, thermal techniques are known for their affectation by vessels in the territory of the electrode.

Ladefoged and Peterson (38) measured renal blood flow in hypertension. There was no difference in flow between those with renal artery stenosis and those without.

2.1.2 Physiology of Cerebral Blood Flow

Cerebral blood flow comprises approximately 14% of the cardiac output and in the normal steady state is relatively constant at 50 - 55 ml/100Gm/minute. Flow in the cerebrovascular bed, as in other organs, is a result of the interplay of two opposing forces, a driving force (blood pressure) and a resisting force - a composite of viscosity of the fluid medium, diameter of the arteriole,and tissue resistance acting upon the nonmuscular capillary.

Kanzow and Diekoff (32) have shown that 50% of the cerebrovascular resistance is regulated in muscular coated vessels. Rodbard (58) using an experimental model has shown that conductance in the vascular bed is regulated at the capillary. It is probable that greater than 80% of the cerebrovascular resistance is related to vessels too small to be seen on angiography. Rodbard further points out that as the capillary has no

musculature, flow is altered by the tissue resistance, capillary pressure and venous pressure. Large vessels at the base of the brain probably play a very small role in the establishment of cerebrovascular resistance and therefore in cerebrovascular conductance.

Poiseuille's law illustrates the relationship between viscosity, pressure and the radius of the lumen. According to this law the major factor in maintaining resistance to flow is the radius of the vessel lumen, providing the tissue resistance is not altered. Thus, change in blood flow reflects change in resistance.

In the normal animal cerebral blood flow remains constant over a wide range of perfusion pressure (20, 21, 36). Cerebral blood flow changes in a linear fashion with change in arterial pCO_2, an increase in pCO_2, effecting arteriolar dilation, decreased resistance and increased flow. The opposite effect occurs with decrease in pCO_2.

Severinghaus (59) and Severinghaus and Lassen (63) have reported that the main controlling factor of cerebral blood flow in the normal animal is the local arteriolar smooth muscle extracellular hydrogen ion concentration.

Following a hypoxic stimulus, autoregulation, i.e. constant flow with change in blood pressure, is abolished to a varying degree. This is also seen when the pCO_2 is increased where flow becomes passively related to change in blood pressure. Although proof is not available it would appear that the controlling factor is now the tissue resistance in this situation.

It is clear, from the results of studies referred to above, that the large vessels at the base of the brain play a very small role in the control of cerebral blood flow.

2.1.3 Significance of Vasospasm

What is the effect of changing the diameter of a large vessel at the base of the brain? In the first instance a pressure differential is created across the constricted segment whereas, in the normal vessel, there is a very small pressure differential from a large artery to a small artery (19). The drop in pressure distal to the constriction will be accompanied by arteriolar dilitation, probably by metabolic means.

Fujishima et al (17) and Zwetnow et al (75) have shown that a lactic acidosis of the cerebrospinal fluid is detectable as the perfusion pressure falls which probably accounts for the maintainence of cerebral blood flow at normal values. Therefore, the resistance distal to the constriction is not limiting.

Denny-Brown (8) has shown that traction on a large cerebral vessel will cause a vasoconstriction up to 2/3 of the control diameter in the area of traction. The artery is not occluded and "providing the circulation is not otherwise compromised no ischemia develops". This is in contradistinction to the diffuse spasm and blanching which can be produced by sudden elevation of intraluminal pressure. In this event sludging and stasis of blood occurs in the arterioles and capillaries and sharply demarcated areas of infarction are evident. "Innervation and the general state of the circulation plays no part in this process". Byrom (5) in studies with Goldblatt preparations has shown that severe spasm of pial vessels occurs during severe hypertension resulting in endothelial damage, ischemia and cerebral edema.

Smith (63) has reported the pathological findings in patients dying of subarachnoid hemorrhage from ruptured cerebral aneurysm without hematoma or gross disruption of cerebral tissue. She found microscopic

infarction in the vascular territories of all the major cerebral vessels with a higher density of lesions in the vascular territory of the aneurysm-bearing vessel, and in this area often becoming confluent.

These findings suggest that a general reduction in blood flow occurs. Diffuse vasospasm relating to vessels too small to be seen on angiography is suggested as the possible cause. Sparing of the central grey masses is against the failure of blood flow being related to spasm at the origin of the vessel. Cerebral edema routinely found in these cases perpetuates the ischemia.

Spasm at the origin may well account for the increase in density of the lesions in the vascular territory of the aneurysm vessel.

Spasm of arterioles and cerebral edema will increase the resistance and introduce the necessary factor such that constriction of the large vessel is significant.

Following elevation of intracranial pressure, such that flow ceases or is decreased markedly, a metabolic acidosis has been shown to occur (17, 75). Froman and Smith (16) have described the biochemical changes occurring in the cerebrospinal fluid following subarachnoid hemorrhage. They found an increase in the hydrogen ion concentration, a decrease in the bicarbonate ion concentration and an increase in lactate. Therefore, one might expect, with the combined effect of the metabolic acidosis and the increase in perfusion pressure as the cerebrospinal fluid pressure decreases following hemorrhage, that an increase in cerebral blood flow might be found.

McQueen and Jelzma (47) have studied the response to subarachnoid injections of blood. They have found that blood, red cell ghosts and other particulate matter cause an acute increase in intracranial pressure,

which is sustained if the blood is injected rapidly so that it spreads over the cortex, but disappears rapidly if infused under gravitational pressure. They propose that this elevation is secondary to occlusion of cerebrospinal fluid flow by plugging of arachnoid villi.

The increased pressure might have an adverse effect on the cortical circulation. Haggendal et al (20) have measured the cerebral blood flow with elevation of the cerebrospinal fluid pressure. This study showed that flow remains constant until the perfusion pressure approaches 50 millimeters of mercury. Following release of the restriction a prolonged elevation of cerebral blood flow occurs. Kety (36) has also shown that cerebral blood flow remains constant until the cerebrospinal fluid pressure approaches 45 centimeters of water.

Since spasm of cerebral vessels does occur after subarachnoid injection of blood one would expect a decrease in cerebral blood flow if spasm was significant.

Zingesser et al (73) have measured regional cerebral blood flow in patients with subarachnoid hemorrhage. A decrease in flow was evident but no correlation was found between cerebral blood flow and the presence or absence of vasospasm. It is noted in Zingesser's results that one patient demonstrating severe diffuse vasospasm had the lowest cerebral blood flow.

James (29) using a single detector has also studied a similar group of patients, dividing these into a 'well' group with mild headache plus or minus mild neck stiffness, and an 'ill' group presenting with altered state of consciousness plus or minus local neurological deficit. He found a significant difference in blood flow between these two groups, and that there was close correlation between the presence or absence of

vasospasm and the magnitude of the decrease in cerebral blood flow. However, it is well known that vasospasm is seen more frequently in the seriously ill patient and a definite conclusion as to the significance of vasospasm cannot be made from this study.

Taylor and Kak (67), utilizing Oldendorf's(52) technique of determining circulation time, using an intravenous injection of radio-iodinated hippuran, have found a prolonged circulation time in patients with subarachnoid hemorrhage demonstrating vasospasm. They have found that patients with prolonged circulation times do poorly if operated upon prior to the circulation time returning to normal. Bohm (2,3) has confirmed this finding in a similar study. That the circulation time is a poor index of cerebral blood flow has been demonstrated by Fieschi (13) and by Zingesser (74). However, studies by Fieschi (13)and by Cronqvist et al (7) have illustrated a poor correlation between circulation time and cerebral blood flow.

Constriction of a vessel when accompanied by an alteration in perfusion pressure will cause ischemia and infarction (8). Constriction of a major size vessel will probably not cause infarction unless other factors are introduced to alter perfusion pressure, viscosity, or other parameters.

Denny-Brown (8) first proposed partial occlusion of a vessel accompanied by a decrease in blood pressure as the mechanism relating to transient ischemic attacks. In their experiments with monkeys, studying the pathophysiology of middle cerebral artery occlusion, infarction did not occur unless a drop in blood pressure was introduced.

Meyer et al (49) have studied the effects of elevating the blood pressure with drugs. It was found in this investigation that cerebrospinal

fluid pressure increases with increase in blood pressure and pial arteries were noted to constrict after transient dilitation. Blanching of the cortex, focal necrosis, and miliary infarcts with small miliary hemorrhages were noted and brain swelling occurred. It would, therefore, appear that spasm of small vessels may be responsible for infarction but it remains to be proven if spasm of major cerebral vessels will reduce flow sufficiently to cause infarction.

2.2 Measurement of Cerebral Flow

2.2.1 Historical Aspects

Studies of cerebral blood flow were infrequent until Kety and Schmidt (37) reported upon a new technique for measuring such flows. The theory of the Kety and Schmidt method was based upon the Fick principle relating the rate of change of inert freely diffusible indicator in a compartment to the flow through the compartment and to the difference in concentration of the indicator in the efferent and afferent vessels. In further studies with this method Kety and Schmidt (36) reported values for normal patients which compare well with values obtained by radioisotope techniques. Kety suggested that the flow could be calculated by studying desaturation of the tissue and, in 1951, proposed the use of radioisotopes.

Lassen and Munck (43) introduced radioactive ^{85}Kr for cerebral blood flow measurements in 1955 utilizing the Kety - Schmidt method.

Lassen and Ingvar in their classic study (28) developed a method of determining cerebral blood flow using Geiger-Meuller counters and radioactive ^{85}Kr.

Landau et al (39) reported values for blood flow in many areas of the grey and white matter as determined by an autoradiographic technique. Values ranging from a low, in the white matter, of approximately 20ml/100Gm/minute to a very high value in the inferior colliculus were found.

2.2.2 Compartmental Analysis

Lassen and Ingvar (28) observed that a semilogarithmic plot of the count rate from the brain versus time could be described by two exponential functions which were attributed to two components of flow:

(i) the "fast" component representative of grey matter

and (ii) the "slow" component representative of white matter

Reivich (57) analyzed the blood flow values, obtained by Landau et al (39) for several areas of the brain, weighting the flows according to the estimated weight of the tissue. He was able to show a strong bimodal distribution of blood flows thus supporting the method of compartmental analysis. Lassen and Ingvar further point out, providing equilibrium of the inert radioisotope is present at the beginning of the washout in all compartments, that mean cerebral blood flow can be calculated from the initial slope of the semilogarithmic replot of the count rate. The advantage of this method is evident in studying cerebral blood flow in rapidly changing conditions. The correlation between mean cerebral blood flow determined by this method, by a compartmental analysis method, or by the stochastic method, overestimates mean cerebral blood flow by approximately 5% in the normal range and these values tend to digress from normal to a greater degree in pathological states than values obtained by the other methods. The initial slope is a good index for studying repeated determinations in one subject where it is difficult to maintain stability.

2.2.3 Stochastic Analysis

Meier and Zierler (48) and Zierler (72) were able to show by statistical methods that the mean transit time of an indicator through an organ is equal to the ratio of volume distribution of the indicator to the flow through the organ.

Hoedt - Rasmussen (23) has demonstrated the relationship between the compartmental and stochastic methods of analysis of cerebral blood flow data.

McHenry (46) and Harper and Glass (18) introduced ^{133}Xe into cerebral blood flow studies. With this radioisotope it was now possible to determine cerebral blood flow utilizing external scintillation detectors.

2.2.4 Initial Slope Method

As calculation of cerebral blood flow by established methods was time consuming Lassen (41, 44) investigated the possibility of determining an index of flow by less sophisticated methods. He noted that the initial two minutes of the semilogarithmic replot of the count rate versus time was usually a straight line and from this, determined an index of mean cerebral blood flow from the slope. As previously noted this value correlates well with values determined by other methods. In an experimental situation flow values are immediately available from a Polaroid picture of the semilogarithmic display of the count rate on a storage oscilloscope.

2.2.5 Physical Characteristics of the Radioisotope

^{85}Kr has the advantage of a long shelf life but has the disadvantage of being an almost pure beta (β) emitter.

^{133}Xe has a greater solubility in oil and water than ^{85}Kr and emits gamma

radiation. The major disadvantage of ^{133}Xe is the low energy of the gamma-ray emmission which creates a problem in 'depth' resolution. Potchen (56) and Wilkinson et al (70) have shown that the best 'depth' resolution is obtained with a discriminator setting of 77 Kev at which value a marked decrease in counting sensitivity is encountered.

To obtain statistically acceptable results for cerebral blood flow, administration of the indicator must be into the internal carotid artery. Common carotid injection results in a systematic error of approximately 13% (23).

The problem of recirculation has been discussed by Hoedt - Rasmussen et al (24). With normal lungs and normal ventilation 90% of the ^{133}Xe is cleared during the first passage through the lungs. The remaining 10% is distributed in the total cardiac output and only 14% of the recirculating activity is distributed to the detector field of view.

2.2.6 Effects of Altering Physiological Parameters

A large volume of literature is available concerning the change in cerebral blood flow that occurs with change in carbon dioxide tension. Hoedt - Rasmussen (23) has shown, in humans, that a linear relationship exists between pCO_2 and cerebral blood flow. For each millilitre change in pCO_2 there is a 2.5% change in cerebral blood flow in the same direction. This relationship holds for pCO_2 values between 20mm and 80mm Hg.

James et al (30) have found a nonlinear relationship between hypercapnia, hypocapnia and cerebral blood flow in baboons, there being a greater effect with hypercapnia.

In pathological conditions with hypoxia or decrease in substrate the relationship between flow and pCO_2 is altered. One cannot estimate the degree of variation that might occur. Therefore, to estimate the effect of one parameter on cerebral blood flow the oxygen and pCO_2 must be held constant.

CHAPTER 3

MATERIALS AND PROCEDURES

3.1 Dispensing of Xenon Gas

^{133}Xe as gas (pressure 5 centimeters mercury, volume 5 - 10 millilitres) was obtained from Oak Ridge National Laboratory in either break-seal vials or in stainless steel cylinders equipped with a valve. The ^{133}Xe gas dispensing system (Figure 1) comprised a stainless steel 60 - 70 ml syringe connected to a sealed system of valves and connecting (type 316) stainless steel tubing with an attached reservoir of preboiled, de-aerated saline.

Prior to autoclaving the dispensing system was dismantled and carefully cleaned. After standard autoclaving procedures the assembly of the device was performed aseptically.

Following assembly, pre-evacuation of the system was carried out and the ^{133}Xe gas then released into the syringe. After allowing 10 minutes for diffusion equilibrium the system was filled with saline which was then dispensed into 15 cc pre-evacuated rubber stoppered glass vials.

This particular dispensing system permitted from 80 to 90% recovery of the radioactive ^{133}Xe gas in vials with specific activities in the range 3 to 20 millicuries per cc of saline.

In animal experiments no further processing of the ^{133}Xe was carried out, however, in clinical studies the vials of ^{133}Xe in saline were again autoclaved and checked periodically by inoculation of blood auger plates.

The efficiency of ^{133}Xe extraction of the above described system is probably superior to other devices which have been described previously in the literature.

3.2 Surgical Methods

Female rhesus monkeys weighing 2.7 to 6.7 kilograms were used in the present investigation. The animals were imported from India and quarantined in New York for 55 days before acquisition. Four animals were obtained from another clinical investigator in our area. On arrival here, initially, no medication was given. However, after one animal had succumbed from pneumonia the evening of arrival each animal acquired subsequently was given 2 cc's of combined procaine and benzathine penicillen. No other medication was given.

On the day of experimentation the animals were given sodium pentabarbitol, 30 milligrams per kilogram intraperitoneal which permitted handling, transportation of the animal to the laboratory, and initial procedures requiring light anesthesia. The animal was intubated and ventilated artificially using a nitrous oxide-oxygen mixture in a ratio of 2:1. Tidal volume was adjusted to maintain carbon dioxide tension as near normal as possible. The animal was paralyzed with curare and maintained in that status with increments as required. Temperature was monitored by an esophageal thermometer and maintained between 36 and 37.5° C by infra-red lamp.

An 18-gauge teflon cannula with a steel needle obturator was positioned in the lumbar subarachnoid space as for routine lumbar puncture. The arterial pressure was monitored continuously by femoral cannula. A venous cannula was positioned in the femoral vein for injection of curare and for monitoring venous pressure in the inferior vena cava. All pressure lines were connected to physiological transducers*. Lead 2 of the

---

* Statham 23 db

ECG was monitored continuously. Three monopolar EEG leads were connected in a fixed relationship with the scintillation detector on the side of injection of the radioisotope used in the cerebral blood flow study. A time constant of 0.3 seconds was used for EEG recording with a high frequency cutoff of 33 cycles per second. All of the above physiological parameters were recorded on a Beckman type RS 8-channel Dynagraph recorder with a 24 lead selector EEG panel. Data was also recorded in parallel on 1/2 inch FM tape.

A 20-gauge teflon cannula was inserted into the common carotid artery, usually on the right side, and guided into the internal carotid artery under fluoroscopic* control. The position of the cannula was confirmed by a single angiogram with Meglumine iothalamate (Figure 2). In the various experiments reported upon in this thesis branches of the external carotid artery were not tied. It was subsequently found that extracranial contamination greater than that expected from recirculation was encountered and in experiments performed after this time extracranial branches were tied. In the initial stages of these studies attempts were made to cannulate the lingual artery. This latter technique has been used with success by other investigators, (42, 30) however, in our hands it met with frequent technical failure. It was also found that probable occlusion of the internal carotid artery was encountered if the cannula was threaded too high. It was noted that if an obturator was not used that tearing of the intima probably occurred resulting in possible emboli formation. Immediately upon insertion of the cannula into the common carotid artery it was flushed with saline containing heparin (5000 units per 500 cc). All other catheters were similarly flushed, periodically, throughout the experimental study.

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* Phillips Bv 20. TV image intensifier

3.3 Administration and Detection of the Radioisotope

One half to one millicurie of ^{133}Xe dissolved in 0.5 cc's to 1 cc of saline was injected over a 2 - 5 second interval. The washout of radioactivity was determined using a single scintillation detector* positioned over the parietal central region one inch superior to the external auditory meatus. In the initial experiments when angiography was attempted the cassette was positioned on the opposite side of the head. After this procedure had been abandoned a second detector was used placed symetrically opposite to the first detector. In the initial six monkeys reported upon an attempt was made at cerebral angiography. However, owing to frequent technical failure and the distance of this laboratory from film developing facilities this procedure was abandoned temporarily pending improvement in our geographical location.

The basic detector used in these studies was a scintillation counter with a 1-inch diameter 1/2 inch thick sodium iodide thallium activated crystal. The isoresponse curve for this detector (when collimated as shown in Figure 3) determined with a point source of ^{133}Xe immersed in a water filled lucite phantom with the crystal face a minimum 5 inches from the collimator face is shown in Figure 3. The upper and lower level discriminators of the single channel analyzer were set to include only the 81 KEV photopeak of ^{133}Xe. This is illustrated diagramatically in Figure 4. The electronic circuitry is illustrated in Fig. 5.

Following the common carotid injection of ^{133}Xe, counts were accumulated for 4-second intervals using a 4-input multiplexor and stored in a 400-channel analyzer. The washout curve for one determination is illustrated in Figure 6. In one of the experiments the counts were

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* Harshaw type 4S2X integral line

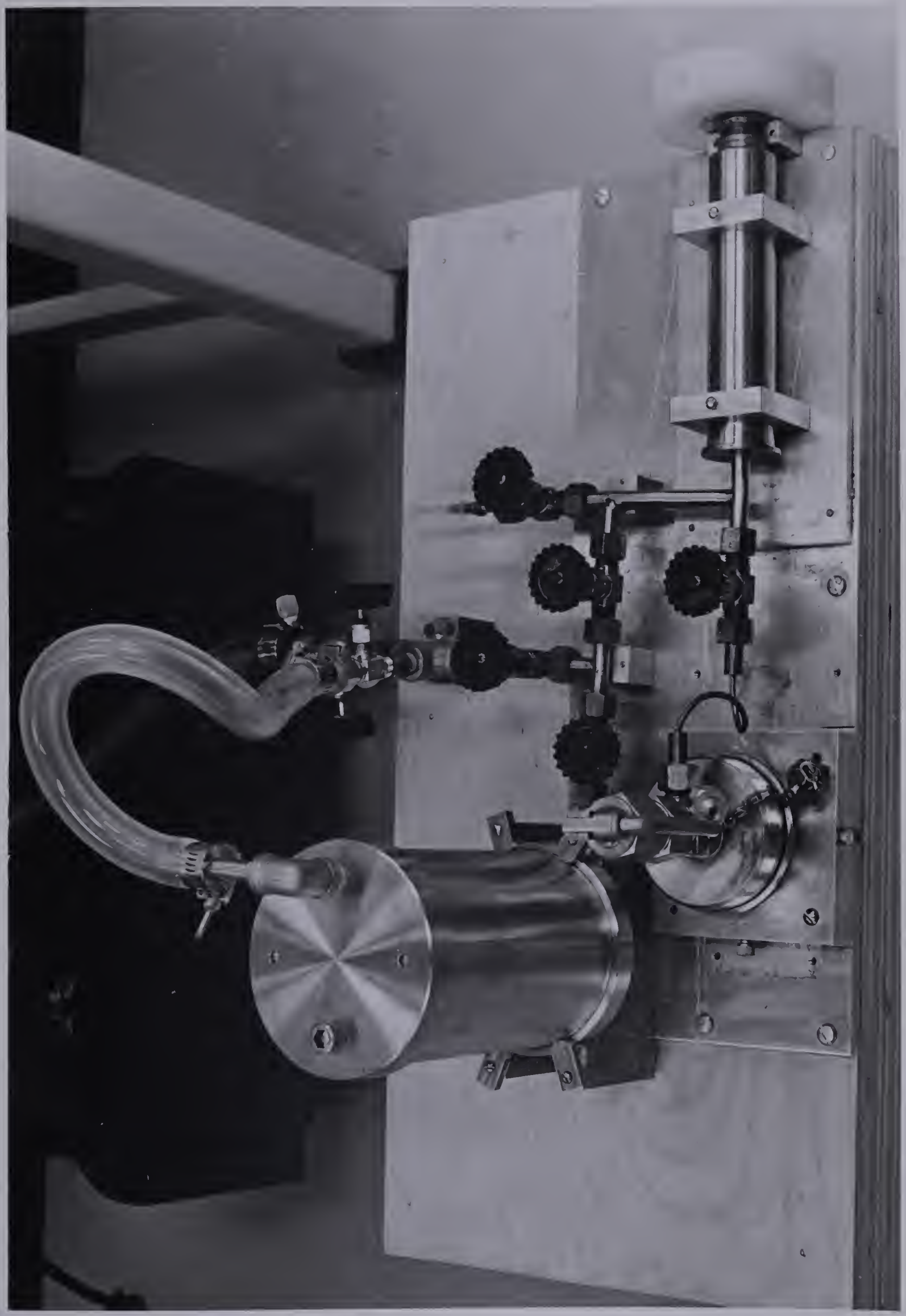


Figure 1

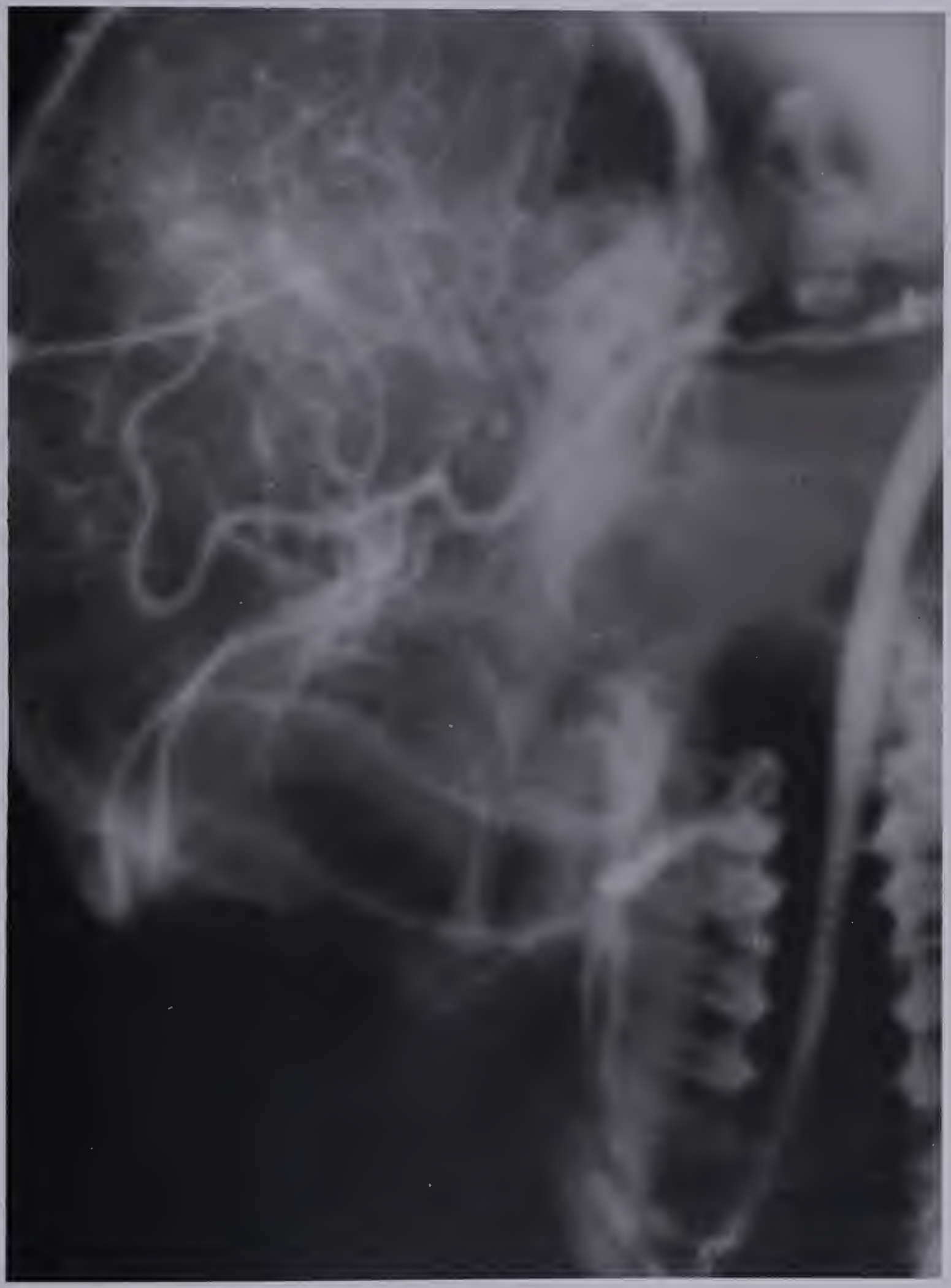
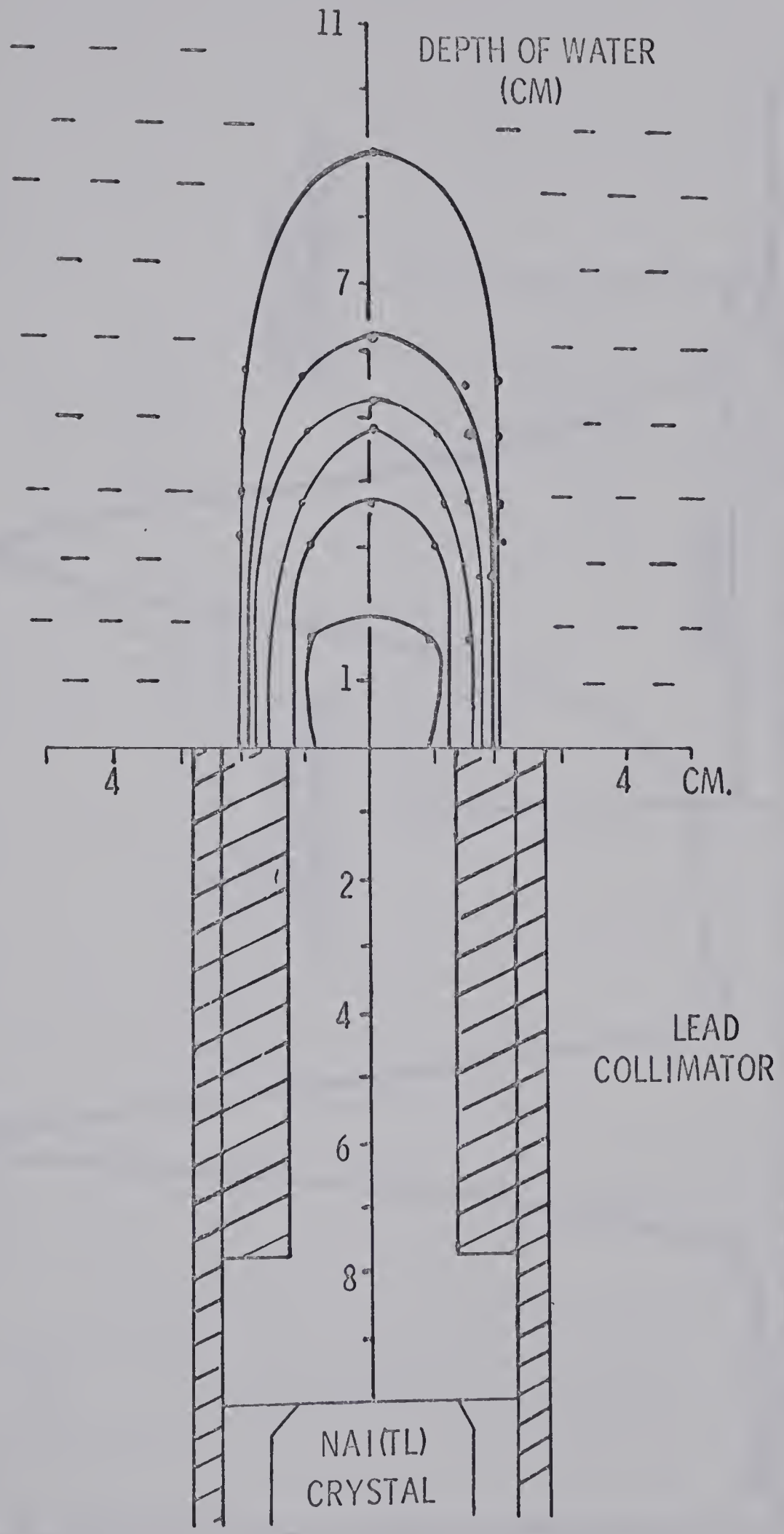


Figure 2



ISOCOUNT CONTOURS AT THE 80, 50, 40, 30, 20, AND 10 PERCENT RESPONSE LEVELS FOR 133XE POINT SOURCE IN WATER

Figure 3

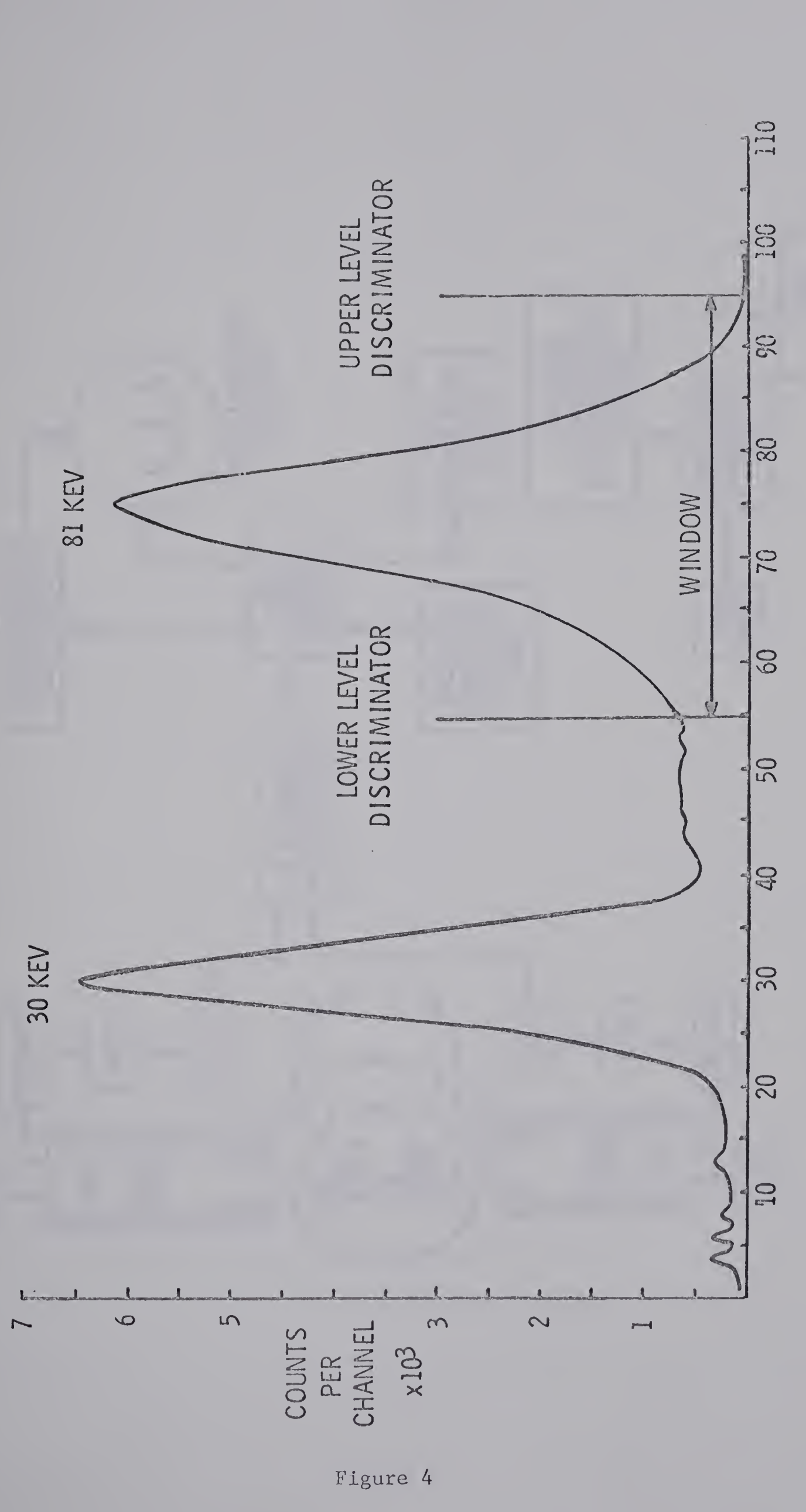

XENON 133 SPECTRUM
30 KEV
81 KEV
LOWER LEVEL DISCRIMINATOR
UPPER LEVEL DISCRIMINATOR
WINDOW
COUNTS PER CHANNEL x10³
CHANNEL NUMBER
7
6
5
3
2
1
10
20
30
40
50
60
70
80
90
100
110

Figure 4

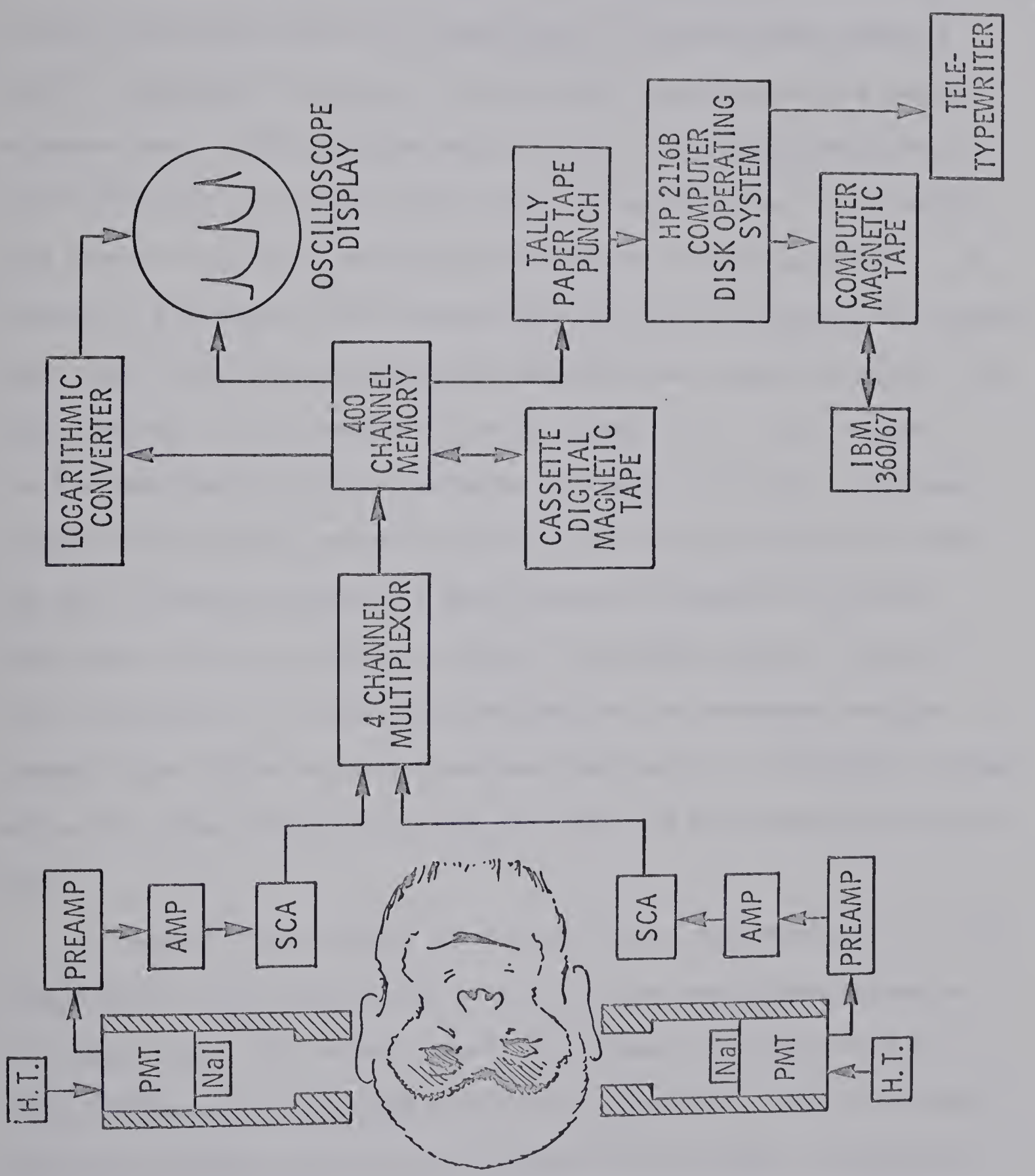

LOGARITHMIC CONVERTER
OSCILLOSCOPE DISPLAY
400 CHANNEL MEMORY
TALLY PAPER TAPE PUNCH
HP 2116B COMPUTER DISK OPERATING SYSTEM
TELE-TYPEWRITER
CASSETTE DIGITAL MAGNETIC TAPE
COMPUTER MAGNETIC TAPE
IBM 360/67
4 CHANNEL MULTIPLEXOR
PREAMP
AMP
SCA
H.T.
PMT
NaI

Figure 5

accumulated at 0.5-second intervals for the initial 200 channels to observe the characteristics of the initial part of the curve. Immediately prior to a particular flow study 40 channels of "remaining activity" from the previous flow were counted for subtraction of this anomalous response from the subsequent flow data. In the initial experiments this latter procedure was not followed; the method used in these cases being due to Lassen (44) where a constant count value, determined from 3 to 4 points just prior to injection, was subtracted from the following response. At the end of a particular flow the counting rate data was dumped onto punched paper tape which could be processed immediately on a small laboratory computer located in the immediate vicinity (Appendix A). This computer facility was found to be very valuable providing, as it did, immediate results for 3 distinct methods of blood flow calculation from the counting data, allowing experimental modifications as changes take place. These data were then written on computer compatible magnetic tape for later processing on a large scale machine* and for permanent storage. A cassette type digital magnetic tape was also used as a backup data storage medium for visual display following the study and for production of copy tapes.

Three to five cerebral blood flow studies were determined in each animal prior to the study of the effects of subarachnoid hemorrhage on such blood flow. One control animal was followed for seven hours for study of flows under prolonged experimental conditions. One particular animal was followed similarly for five hours and was then revived and used in a subsequent study of subarachnoid hemorrhage. The flows were assessed every 30 minutes after the hemorrhage. The results of a typical flow study is illustrated in Figure 6.

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* IBM 360/67

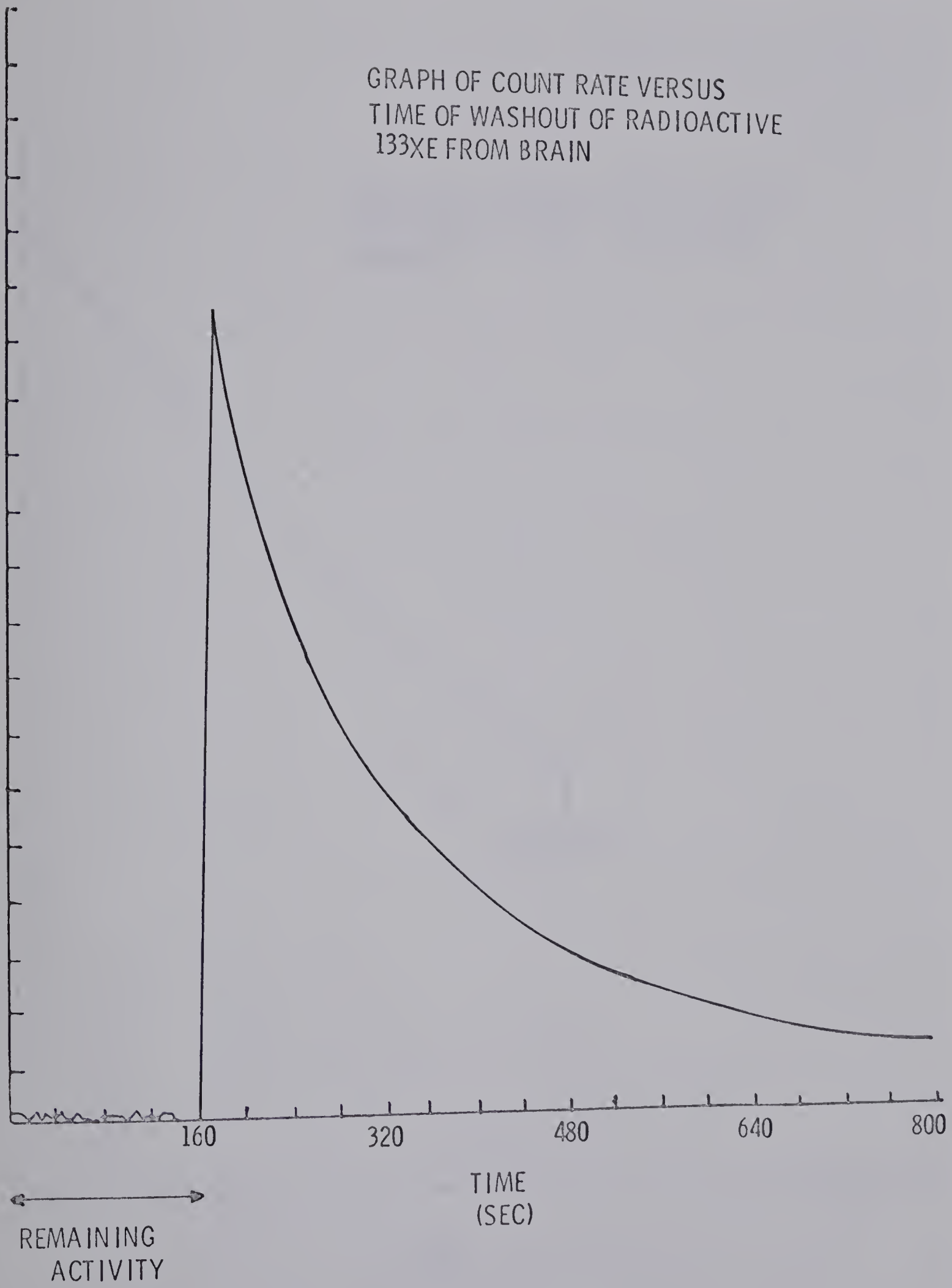

GRAPH OF COUNT RATE VERSUS
TIME OF WASHOUT OF RADIOACTIVE
133XE FROM BRAIN
160
320
480
640
800
TIME
(SEC)
REMAINING
ACTIVITY

Figure 6

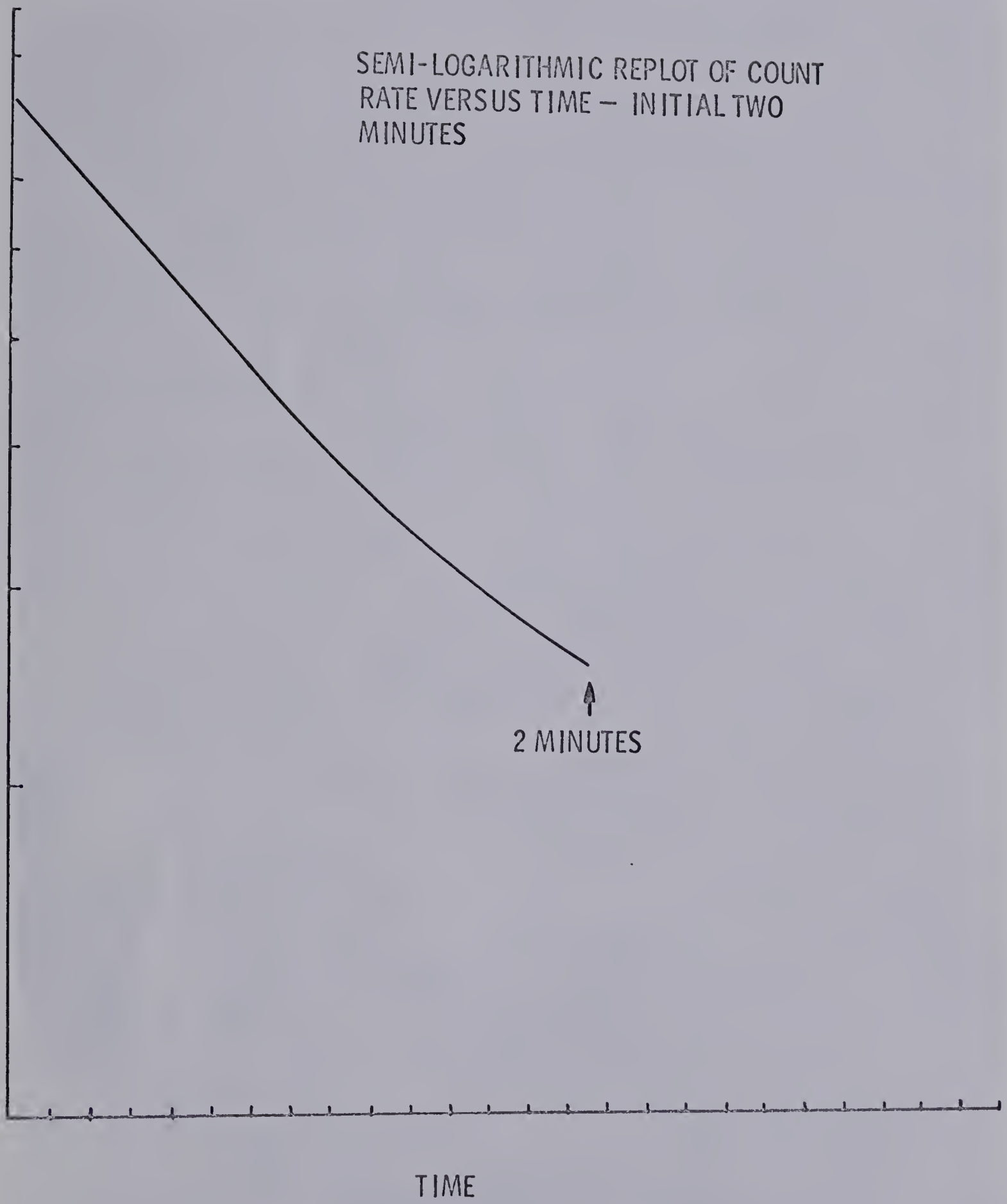

SEMI-LOGARITHMIC REPLOT OF COUNT RATE VERSUS TIME – INITIAL TWO MINUTES
2 MINUTES
TIME

Figure 6a

Figure 7

3.4 Method of Simulating Subarachnoid Hemorrhage

A twist drill hole was made 0.5 centimeters posterior to the nasion. A 20-gauge steel spinal needle was inserted under fluoroscopic control along the base of the skull in the depression between the supra-orbital bones to the level of the anterior clinoid process and into the chiasmatic cistern. Cerebral spinal fluid was observed to return from the needle. In experiments described previously (12) this procedure was found adequate for inducing subarachnoid hemorrhage around the cerebral vessels at the base of the brain. An x-ray film was then taken to confirm needle position (Figure 7). Subarachnoid hemorrhage was simulated by injecting 4 cc's of fresh autogenous blood under constant pressure over a 20-second interval. Cerebral blood flows were then measured for a period of 3 to 4 hours following this subarachnoid hemorrhage. The initial flow study started within 3 to 5 minutes of the hemorrhage.

At the end of each experiment the animal was given oxygen, paralysis was reversed with neostigmine and the animal aroused for a brief gross neurological examination. The animal was then sacrificed with an overdose of sodium pentabarbitol and autopsy was carried out either immediately or the following morning. Photographs were taken of the brain which was then fixed in formalin and examined closely after standard cutting. Histological examination was not carried out.

3.5 Calculations

Three methods of analysis of the biological decay curve have been described. These are briefly reviewed individually in the following section. For a more detailed discussion of these methods see Appendix B. A Fortran program incorporating the three methods is shown, with flow chart and computer output, in Appendix C.

3.5.1 Compartmental Analysis

Ingvar and Lassen (28) recognized that the semi-logarithmic replot of counting rate of the biological decay curve could well be described by two components representing a fast compartment and a slow compartment which in turn have been interpreted as representing flow in the grey matter and flow in the white matter respectively. This method of analysis has been tested (24, 50, 56, 57) and found to be valid. Recognizing that the intercept of initial count rate in each compartment was related to the relative weight of that compartment a mean value of cerebral blood flow in milliliters per hundred grams per minute could be calculated from the intercepts and slopes for each component. The goodness of fit was tested by inscribing, on a semi-logarithmic replot of the decay curve, the values obtained from the computer program for intercepts and slopes. It was found that as flows were repeated the background count increased to a plateau during the time interval of the first 3 or 4 flows. The correction for this non-zero starting point was described above, viz., either by subtracting a constant value for "remaining activity" as obtained from initial points before injection of the radioisotope, or by subtracting an exponential function describing the remaining activity as obtained from the 40 points accumulated before injection of the radioisotope for a subsequent flow study. Both of these methods proved satisfactory for correction of the counting rate decay curves.

3.5.2 Stochastic Analysis of Counting Rate Data

Zierler (72) has formulated a method for calculating mean cerebral blood flow without making any assumptions for homogeniety of tissue or constancy of equilibrium of radioisotope in blood and tissue. He has

shown that the mean transit time of the indicator through the system is the ratio of the volume in which tracer is distributed to the blood flow from the system. The mean transit time of the indicator is also equal to the integrated area under the curve of count rate versus time, divided by the peak or zero time value of the count rate. The mean cerebral blood flow is therefore calculated from the ratio of the peak or zero time value divided by the area under the curve of count rate versus time.

3.5.3 Initial Slope Method

Lassen (41, 44) showed that an index of mean cerebral blood flow could be calculated from the initial slope of a semilogarithmic replot of the ^{133}Xe washout curve if the concentration of ^{133}Xe in all compartments of the heterogenous tissue was the same. The initial part of the curve, when displayed as a semilogarithmic plot (Figure 6a) is a straight line and can therefore be represented by a mono-exponential function. As the initial part of the curve is dominated by the fast components, the mean cerebral blood flow is calculated utilizing the partition co-efficient for grey matter. A good correlation between the initial slope method for estimation of mean cerebral blood flow, the calculation by the Stocastic method of Zierler, or by the compartmental analysis technique of Lassen has been found by several investigators (25, 56, 70). In the present study the initial slope was initially measured from a storage oscilloscope display of the semilogarithmic count rate versus time plot however, a calculation of this latter parameter, from the first 60 seconds of the decay curve, was later incorporated into the computer program. The partition co-efficients for ^{133}Xe in grey and white matter were calculated according to the method of Mallett and Veall (71) using the solubilities

of ^{133}Xe in the grey and white matter of baboons (James 30). Each of these latter values were corrected for hematocrit. A mean partition coefficient for the brain was calculated on the basis of a 52 - 48 ratio of grey matter to white matter.

Mean cerebral blood flow values were corrected to a carbon dioxide tension of 40 millimeters of mercury using the correction formula as described by Hoedt - Rasmussen (23). This correction factor applies to humans and is probably invalid since James (30) has determined a different reactivity of cerebral vessels, in baboons, to alterations in carbon dioxide tension.

The EEG was interpreted as to frequency and amplitude. Formal frequency analysis was not done. The ECG was interpreted by the standard methods.

CHAPTER IV

RESULTS

4.1 Cerebral Blood Flow After Induced Subarachnoid Hemorrhage

Figure 8 illustrates mean cerebral blood flow, under experimental conditions, over a six-hour period. Excluding the initial and final values, cerebral blood flow ranged from 38 to 65 ml/100Gm/minute. Flow is seen to follow changes in pCO_2 but does not passively follow changes in blood pressure. At the termination of this experiment the animal was readily aroused without neurological deficit and was used in the following day's experiment.

Figure 9 illustrates the results of a similar study. When this particular experiment was terminated the animal was readily aroused and showed no gross neurological deficit. However, post-mortem examination revealed a large intracerebral hemorrhage in the left globus pallidus and the parieto - occipital cortex. In this particular animal the mean cerebral blood flow was markedly reduced at 120 minutes and remained so for the remainder of the experiment. Cortical activity remained in the EEG and cortical blood flow remained above 65ml/100Gm/minute for seven hours. It is not clear if infarction occurred at 120 minutes and cerebral hemorrhage occurred during the elevation of blood pressure when subarachnoid hemorrhage was induced at the end of seven hours.

The results of seven experiments in which subarachnoid hemorrhage was induced are illustrated in Figures 10 to 16.

The relationship between cerebral blood flow, pCO_2, cerebrospinal fluid pressure and blood pressure can be seen over the time course of the experiment. Cerebrospinal fluid pressure is not recorded in all animals because of failed lumbar puncture.

The change in blood pressure and cerebrospinal fluid pressure during the actual hemorrhage is illustrated on a two-minute time base.

In two animals there was a significant decrease in cerebral blood flow (Figures 10 and 11). In one animal (Figure 10) this was associated with a marked decrease in perfusion pressure; the following flow, at thirty minutes, is slightly higher but remains significantly reduced.

In another animal (Figure 11) the cerebral blood flow is reduced significantly from the pre-subarachnoid hemorrhage value. However, in this animal the carotid cannula had to be changed from the right to the left carotid after one hour and the prehemorrhage values may reflect a posthypoxic hypermia.

In five animals the mean cerebral blood flow was not significantly altered in the first hour following subarachnoid hemorrhage (Figures 12, 13, 14, 15, and 16). In one animal there was an increase in cerebral blood flow in the first hour after the subarachnoid hemorrhage which was not significant (Figure 13).

In all animals with subarachnoid hemorrhage there was a gradual but significant reduction in cerebral blood flow occurring one to three hours after hemorrhage frequently accompanied by an elevation of systemic blood pressure (Figures 13 and 14). A secondary rise in cerebrospinal fluid and blood pressures associated with a marked decrease in cerebral blood flow was found in one animal (Figure 12).

4.2 Cerebral Blood Flow and the EEG

Only three monopolar tracings were obtained from needle electrodes positioned anterior, posterior and central in relation to the scintillation

detector. At the beginning of the experiment, and lasting approximately three hours, the tracings were consistent with barbiturate anesthesia with slowing but good amplitude and with good fast activity gradually replacing the slow activity. This was associated with an increase in the mean cerebral blood flow.

During the induction of subarachnoid hemorrhage the tracing became flat at fifteen to twenty seconds when the cerebrospinal fluid pressure exceeded or approached mean blood pressure. The tracing remained flat for seventeen to twenty seconds and activity returned in the form of giant slow waves of frequency one to one and one half per second, with amplitudes of 100 to 200 microvolts. The tracing reverted to the prehemorrhage state in one to three minutes providing cerebral blood flow had been normal prior to hemorrhage.

Throughout the remainder of the experiment there was a gradual slowing of the EEG followed by decrease in the amplitude. The changes in the EEG over the time course of a typical experiment is shown in Figure 18a to 18d. In the control animal (Figure 17) fast activity remained during the six-hour period with random slow waves of frequency in the theta range.

In many animals thought to be healthy at the time of the induced subarachnoid hemorrhage it was noted, 60 to 90 minutes after the hemorrhage, that injection of the ^{133}Xe in saline (volume 0.5 - 1 cc) provoked a slowing of the EEG and a transient but significant elevation of the cerebral spinal fluid pressure. The significance of this finding is not known but may reflect cerebral edema.

4.3 Electrocardiograms

The ECG changes observed following subarachnoid hemorrhage have been discussed by others (22, 51). In this experiment, changes observed include:

1. increased amplitude of the T wave
2. ST elevation or depression
3. sinus arrythmia
4. sinus pause
5. nodal rhythm and extrasystoles
6. ventricular extrasystoles
7. ventricular tachycardia
8. prolonged QT interval

The ECG changes were transient lasting only a few seconds with the exception of T wave changes which were often prolonged lasting, at times, to the termination of the experiment. Axis shifts were noted but as only one lead was recorded no further interpretation is possible.

4.4 Blood Pressure and Cerebrospinal Fluid Pressure

In each animal studied the blood pressure increased during the first hour as the effect of the barbiturate disappeared. During the hemorrhage the cerebrospinal fluid pressure increased to a maximum at twenty seconds, exceeding systemic blood pressure in most cases, and rapidly decreased to the prehemorrhage level in 2 - 3 minutes. The blood pressure increased with elevation of the cerebrospinal fluid pressure to a maximum at forty seconds and rapidly declined to the prehemorrhage level. In three animals an initial decrease in blood pressure occurred with the minimum value corresponding to the maximum cerebrospinal fluid pressure.

4.5 Postmortem Results

Only gross examination was carried out. Results from similar experiments, including histological examination, have been reported previously (76).

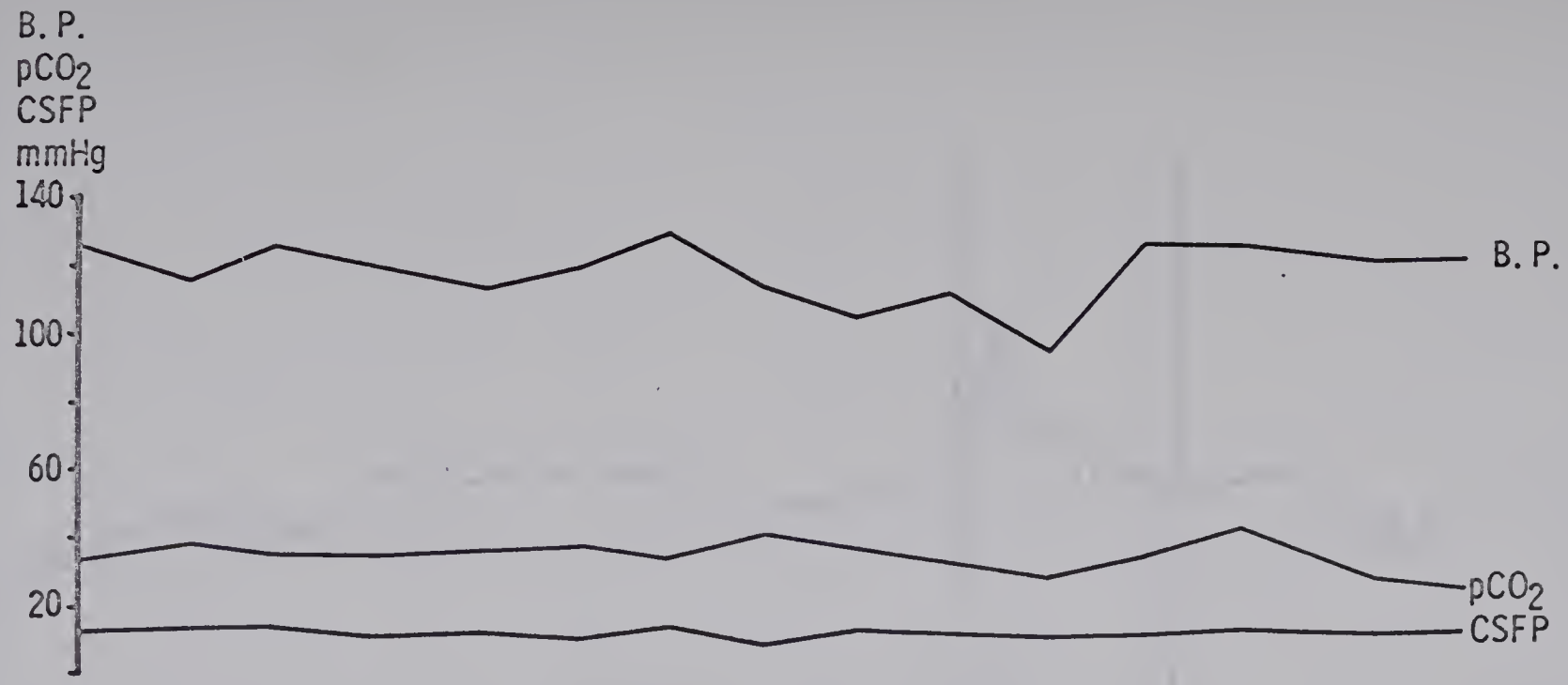
Figures 19 and 20 illustrate the extent of the subarachnoid hemorrhage at the base of the brain and over the cerebral mantle. Considerable variation in the extent of hemorrhage was noted and frequently the blood was minimal over the hemispheres. Hemorrhage was present around the base and in contact with the major cerebral vessels in all animals. Coronal sections revealed a hemorrhagic infarct in only one animal (Figure 21). In the animals discussed in this thesis no other gross lesion, with the exception of the intracerebral hemorrhage, was encountered (not illustrated). Figure 22 illustrates coronal sections from frontal to occipital. There was no hernial notch in any of the brains. No brain stem lesions were found except those due to the needle placement which are not included in the study.

4.6 Cortical Blood Flow and Mean Cerebral Blood Flow Calculated by the Initial Slope and Height-Over-Area Method from the ^{133}Xe Washout Curve

Figures 8 to 16 demonstrate the parallel between mean cerebral blood flow calculated from the initial slope of the curve and by the method of Zierler (72). Values for cerebral blood flow calculated by these methods generally show good agreement, however, there is frequently a poor correlation at the beginning of the experiment. The correlation is also frequently poor following the hemorrhage, perhaps reflecting a tissue peak which would tend to separate the two values.

The poor correlation during the initial part of the experiment reflects extracranial contamination, which introduces a slow component which will not affect the area under the curve. Thus, the initial slope probably gives a more accurate estimate of the mean cerebral blood flow in this study.

There was poor correlation between the cerebral blood flow calculated from the initial slope and the cortical blood flow calculated from the fast component obtained by compartmental analysis. Occasionally the mean flow (initial slope) exceeded the cortical flow (fast compartment). This probably reflects a poor fit of the curve into two components related to the presence of a third slow component, which in turn results in an underestimate of the fast component. In subsequent experiments (not reported here) the external carotid system was tied thereby excluding the extracranial circulation and a much better fit of the curve into two components was found.


B. P.
pCO_2
CSFP
mmHg
140
100
60
20
B. P.
pCO_2
CSFP

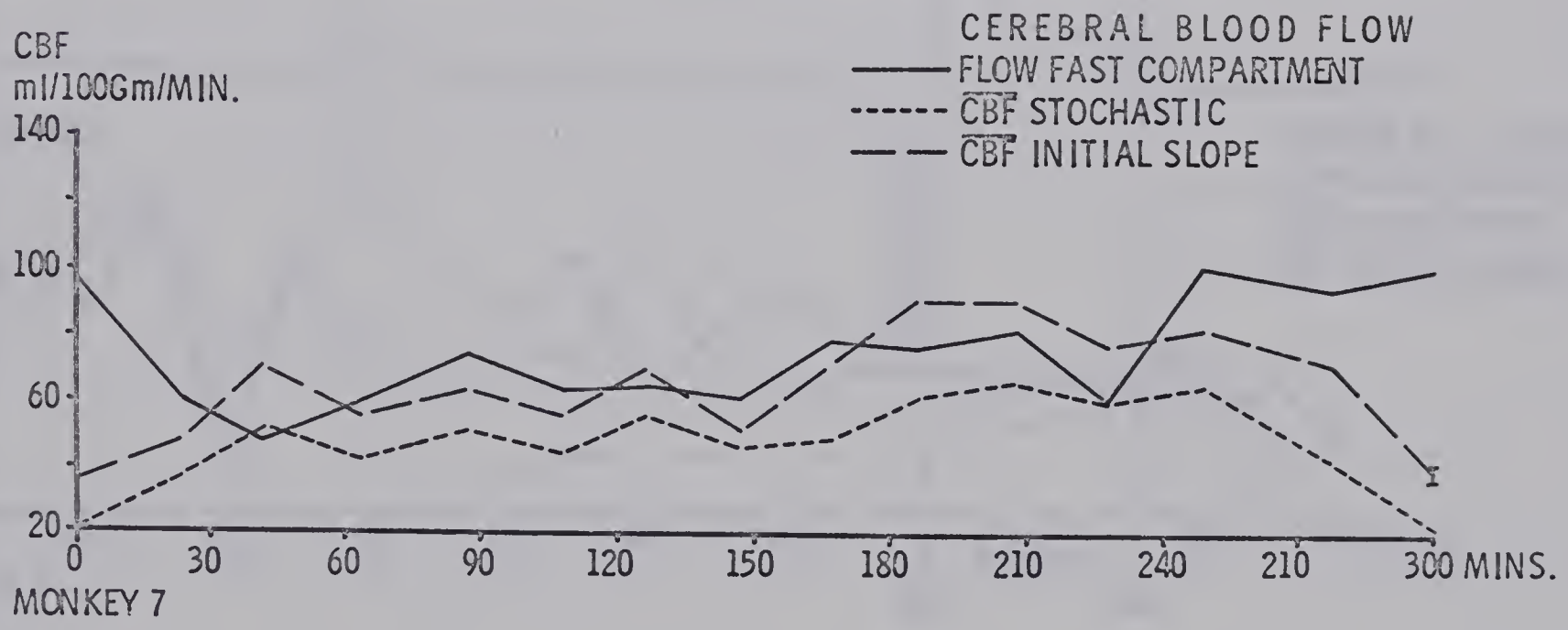

CEREBRAL BLOOD FLOW
FLOW FAST COMPARTMENT
$\overline{CBF}$ STOCHASTIC
$\overline{CBF}$ INITIAL SLOPE
CBF
ml/100Gm/MIN.
140
100
60
20
0
30
60
90
120
150
180
210
240
210
300 MINS.
MONKEY 7

Figure 8

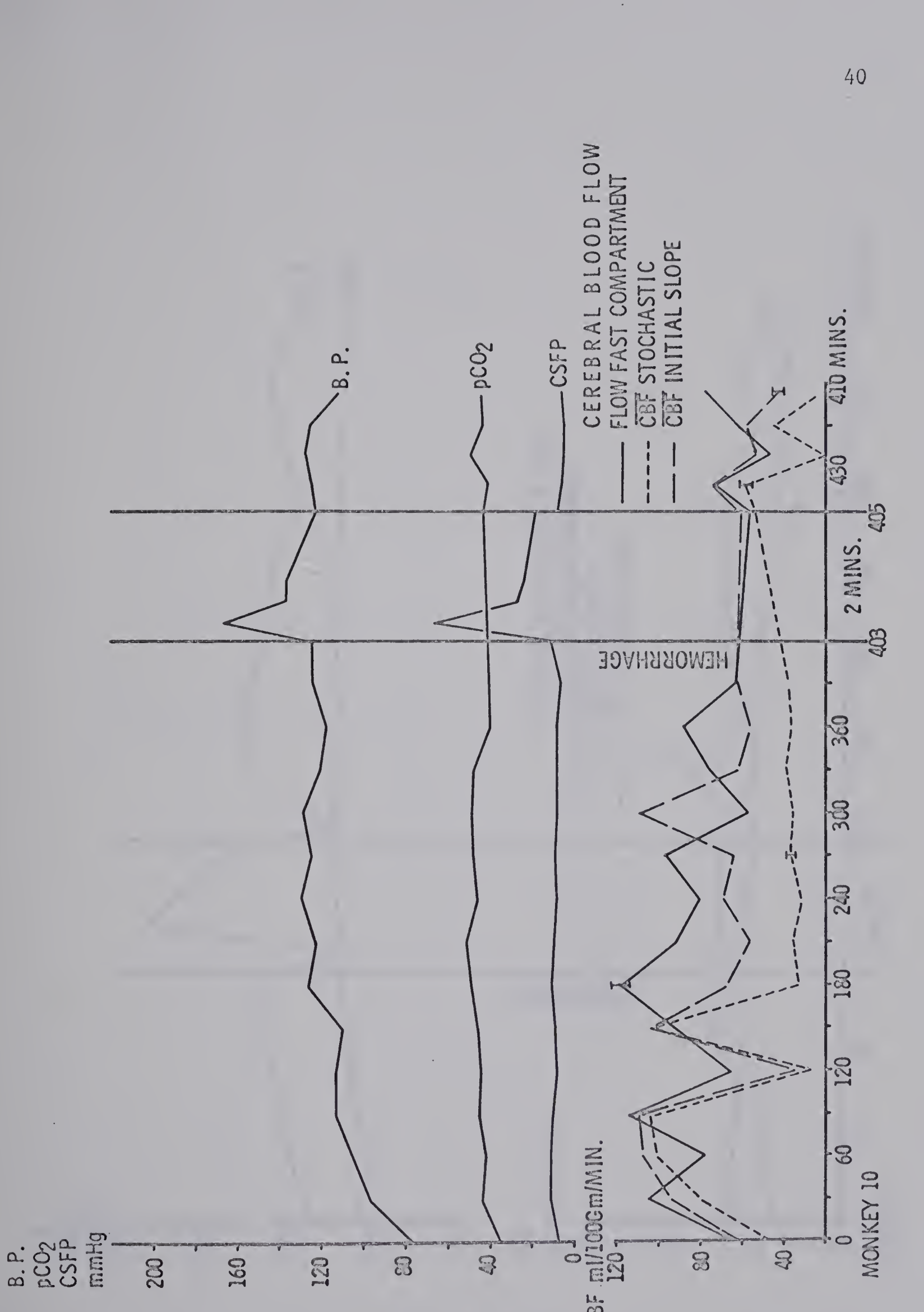

B.P.
pCO2
CSFP
mmHg
200
160
120
80
40
0
CBF ml/100Gm/MIN.
120
80
40
0
MONKEY 10
60
120
180
240
300
360
403
405
430
410 MINS.
2 MINS.
HEMORRHAGE
B.P.
pCO2
CSFP
CEREBRAL BLOOD FLOW
FLOW FAST COMPARTMENT
CBF STOCHASTIC
CBF INITIAL SLOPE

Figure 9

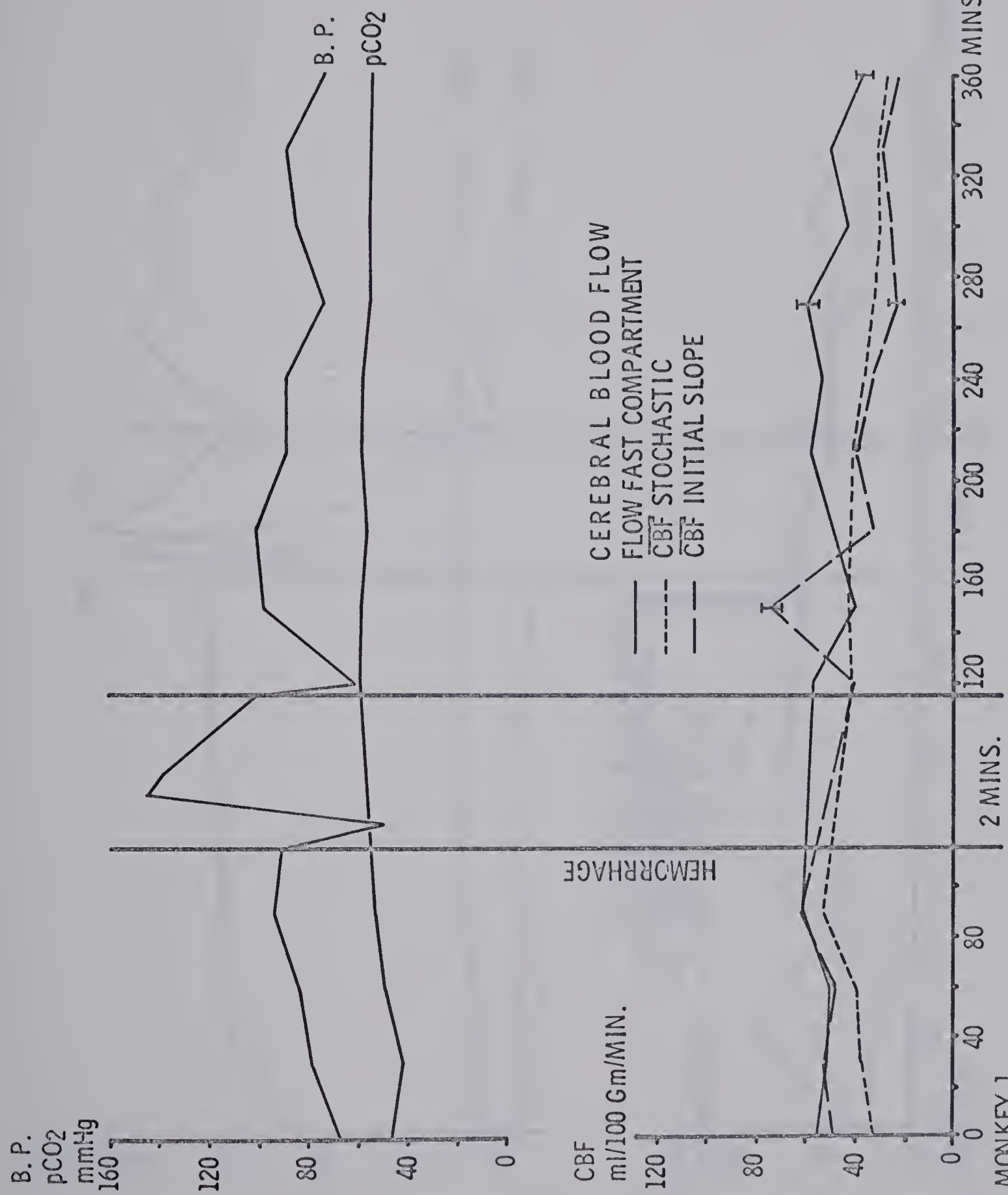

B. P.
pCO2
B. P.
mmHg
160
120
80
40
0
CBF
ml/100 Gm/MIN.
120
80
40
0
HEMORRHAGE
CEREBRAL BLOOD FLOW
FLOW FAST COMPARTMENT
$\overline{CBF}$ STOCHASTIC
$\overline{CBF}$ INITIAL SLOPE
2 MINS.
0
40
80
120
160
200
240
280
320
360 MINS.
MONKEY 1

Figure 10

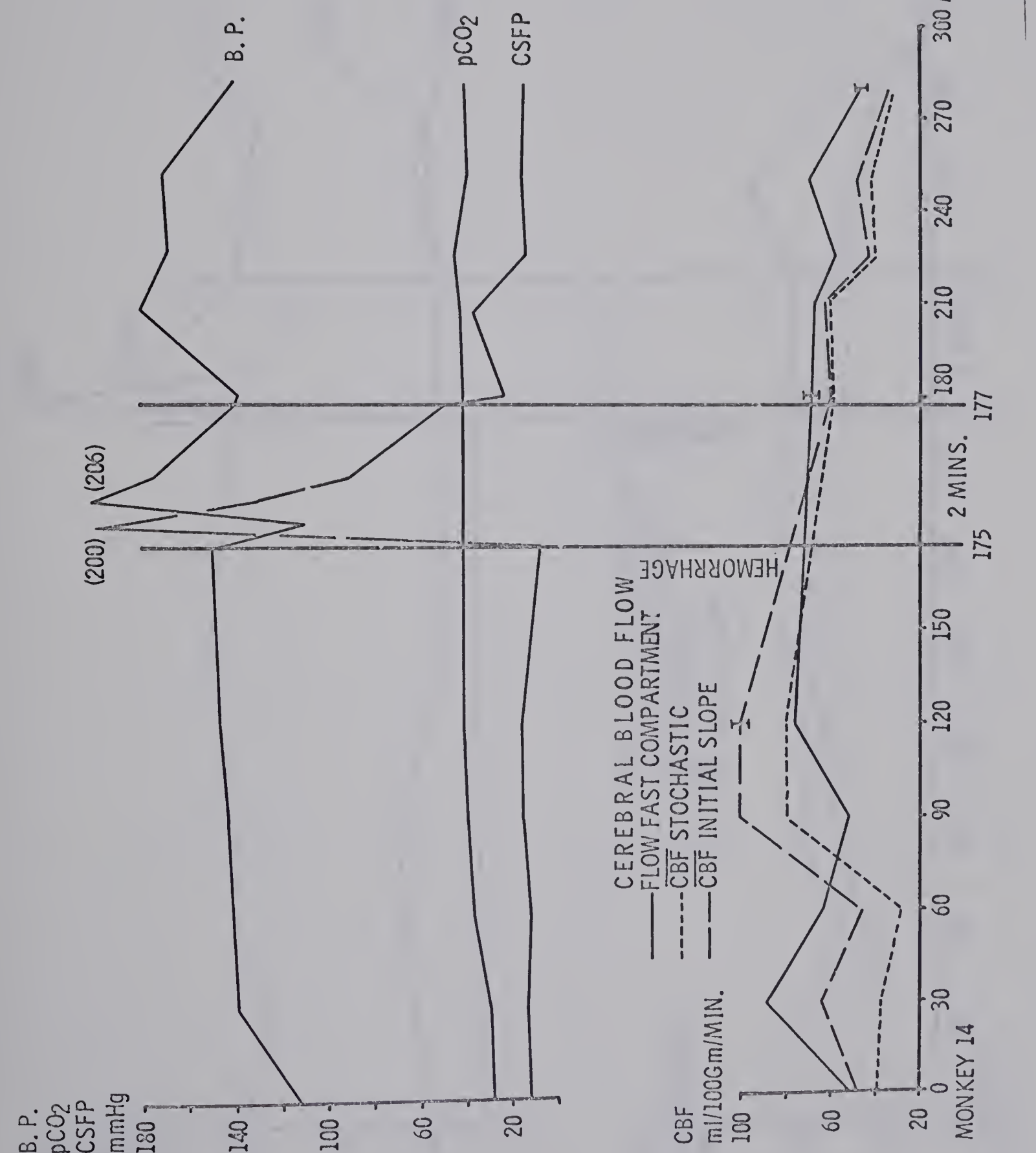

B. P.
pCO2
CSFP
mmHg
180
140
100
60
20
(200)
(206)
B. P.
pCO2
CSFP
2 MINS.
175
177
180
210
240
270
300 MINS.
HEMORRHAGE
CEREBRAL BLOOD FLOW
FLOW FAST COMPARTMENT
CBF STOCHASTIC
CBF INITIAL SLOPE
CBF
ml/100Gm/MIN.
100
60
20
0
30
60
90
120
150
MONKEY 14

Figure 11

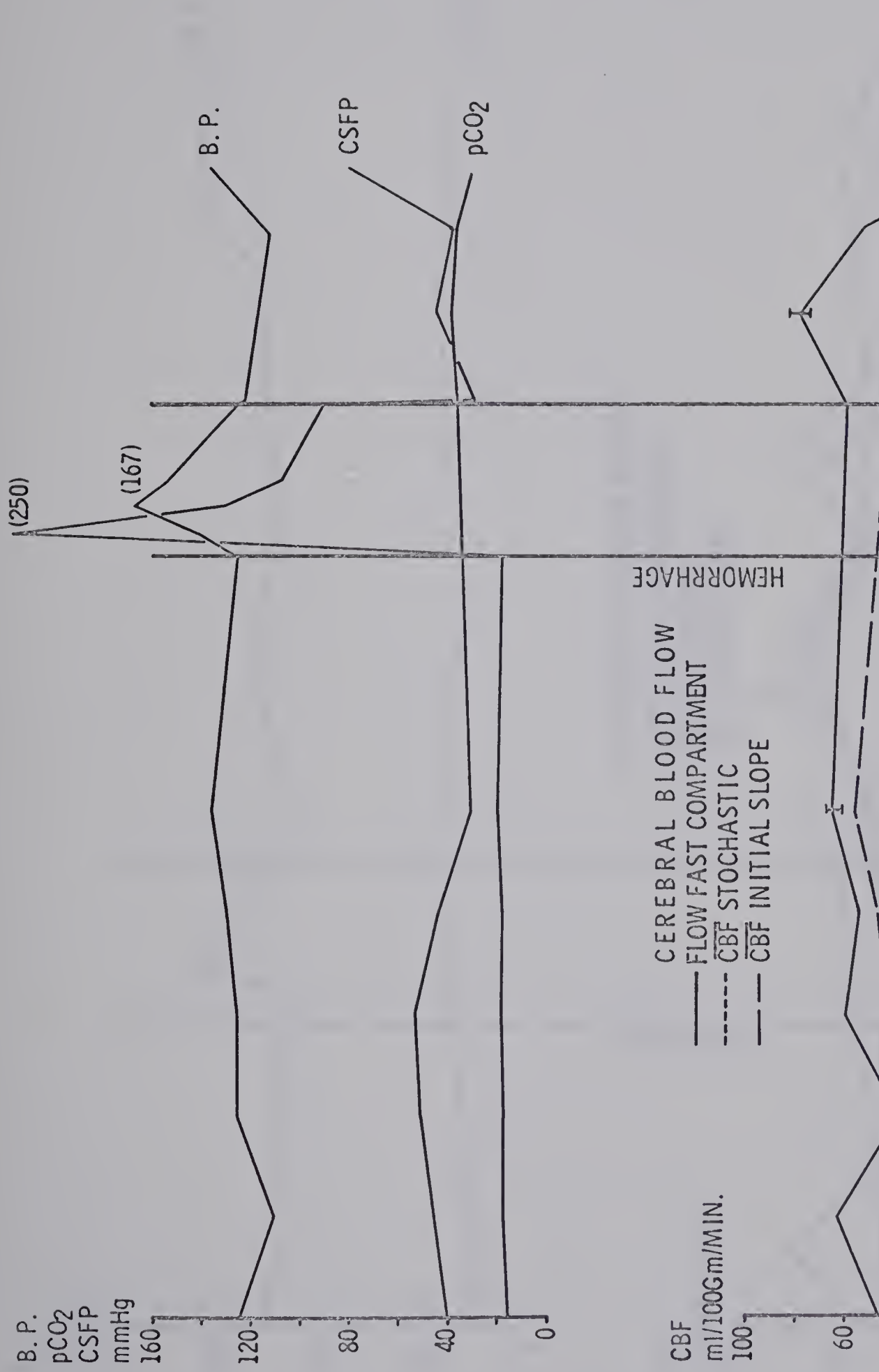

B. P.
pCO2
CSFP
mmHg
160
120
80
40
0
(250)
(167)
B. P.
CSFP
pCO2
HEMORRHAGE
225
2 MINS.
227
210
260
290
320 MINS.
CBF
ml/100Gm/MIN.
100
60
20
0
CEREBRAL BLOOD FLOW
FLOW FAST COMPARTMENT
C̄B̄F̄ STOCHASTIC
C̄B̄F̄ INITIAL SLOPE
20
60
90
120
150
180
210
MONKEY 13

Figure 12

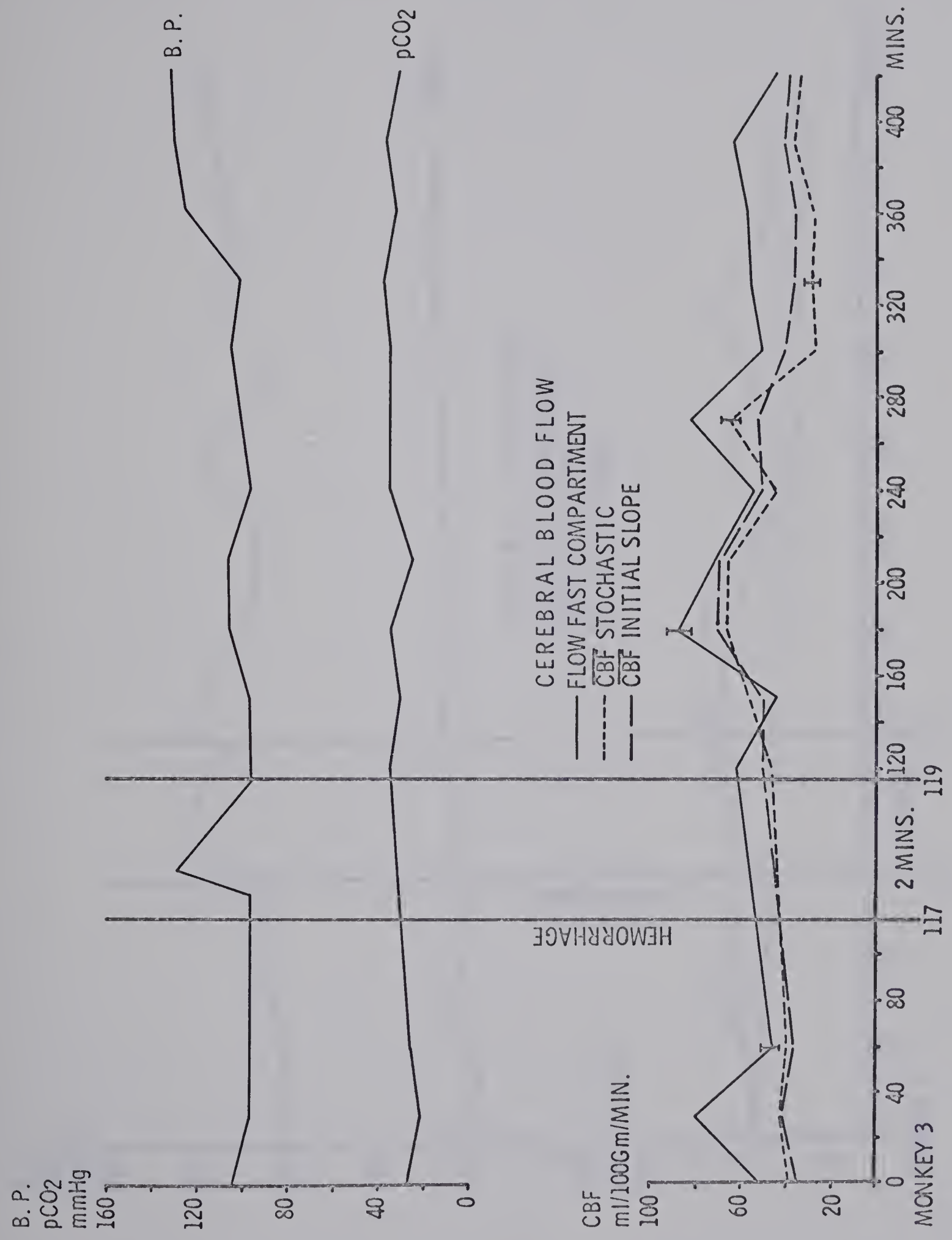

B. P.
pCO2
mmHg
160
120
80
40
0
B. P.
pCO2
HEMORRHAGE
CEREBRAL BLOOD FLOW
FLOW FAST COMPARTMENT
CBF STOCHASTIC
CBF INITIAL SLOPE
CBF
ml/100Gm/MIN.
100
60
20
0
MONKEY 3
117
2 MINS.
119
40
80
120
160
200
240
280
320
360
400
MINS.

Figure 13

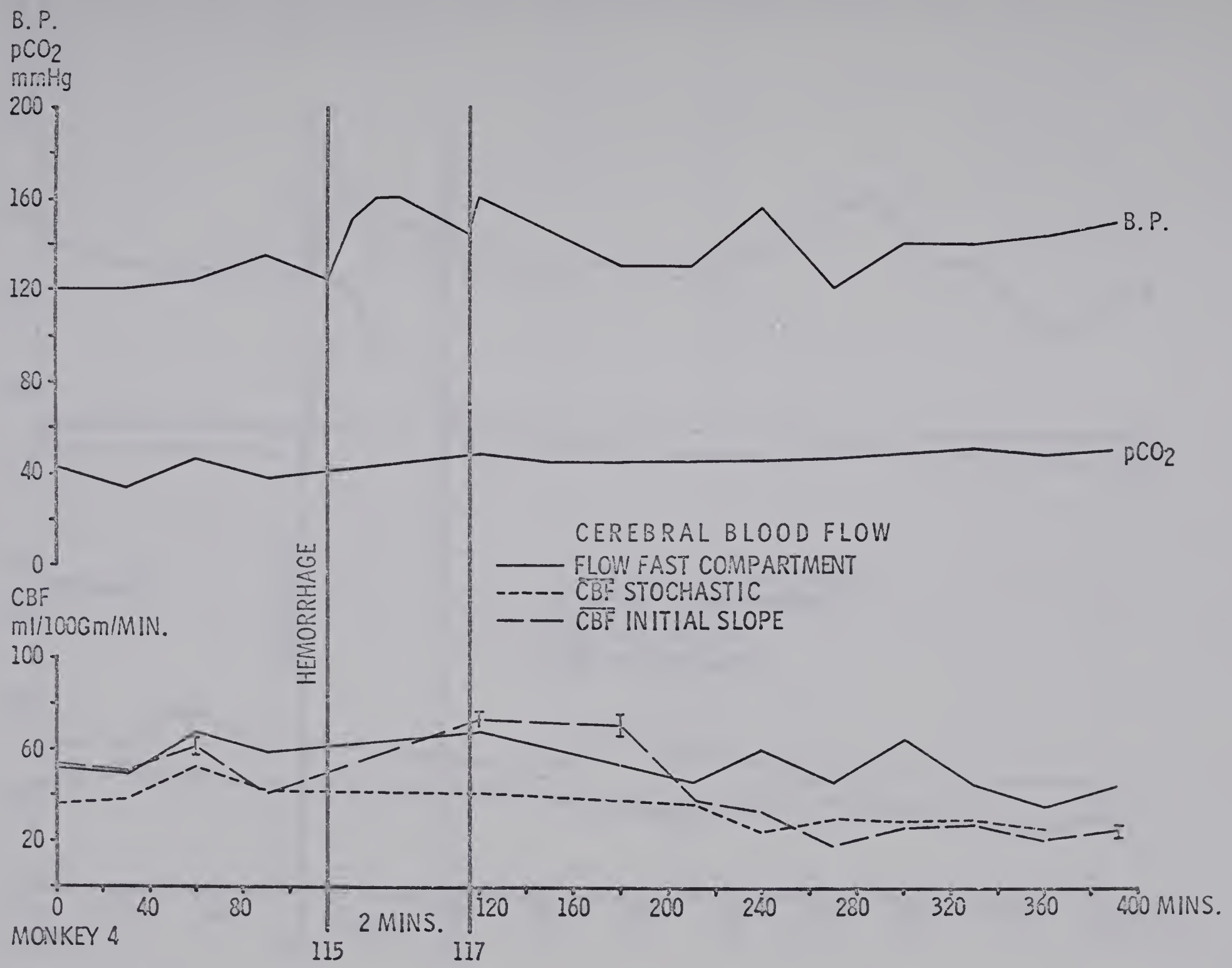

B. P.
pCO_2
mmHg
200
160
120
80
40
0
B. P.
pCO_2
CEREBRAL BLOOD FLOW
FLOW FAST COMPARTMENT
$\overline{CBF}$ STOCHASTIC
$\overline{CBF}$ INITIAL SLOPE
CBF
ml/100Gm/MIN.
100
60
20
HEMORRHAGE
0
40
80
115
2 MINS.
117
120
160
200
240
280
320
360
400 MINS.
MONKEY 4

Figure 14

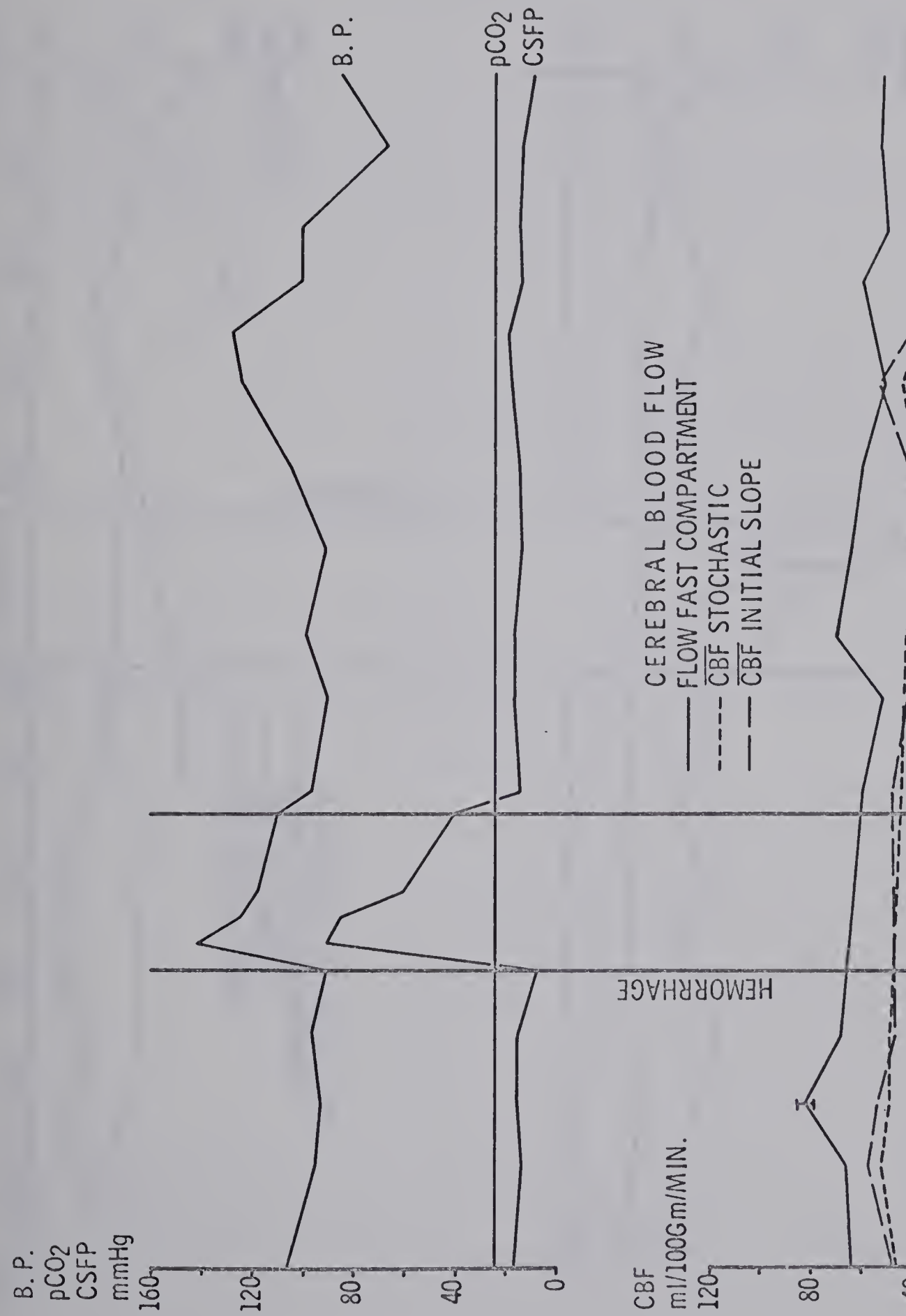

B. P.
pCO2
CSFP
mmHg
160
120
80
40
0
B. P.
pCO2
CSFP
CEREBRAL BLOOD FLOW
FLOW FAST COMPARTMENT
C̄BF STOCHASTIC
C̄BF INITIAL SLOPE
CBF
ml/100Gm/MIN.
120
80
40
0
HEMORRHAGE
0
30
60
87
2 MINS.
89
90
120
150
180
210
240
270
300 MINS.
MONKEY 8

Figure 15

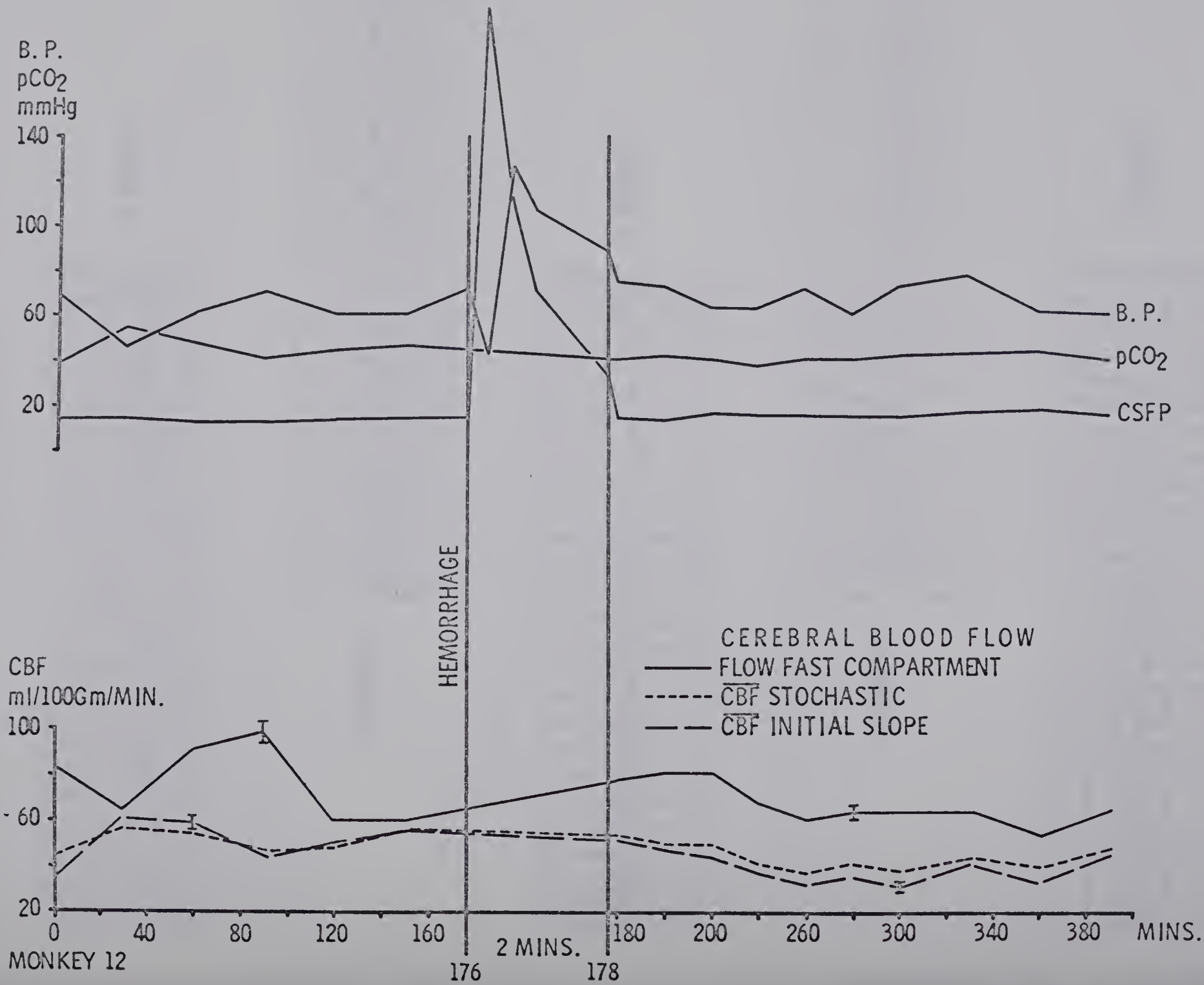

B. P.
pCO_2
mmHg
140
100
60
20
B. P.
pCO_2
CSFP
HEMORRHAGE
CEREBRAL BLOOD FLOW
FLOW FAST COMPARTMENT
$\overline{CBF}$ STOCHASTIC
$\overline{CBF}$ INITIAL SLOPE
CBF
ml/100Gm/MIN.
100
60
20
0
40
80
120
160
180
200
260
300
340
380
MINS.
2 MINS.
MONKEY 12
176
178

Figure 16

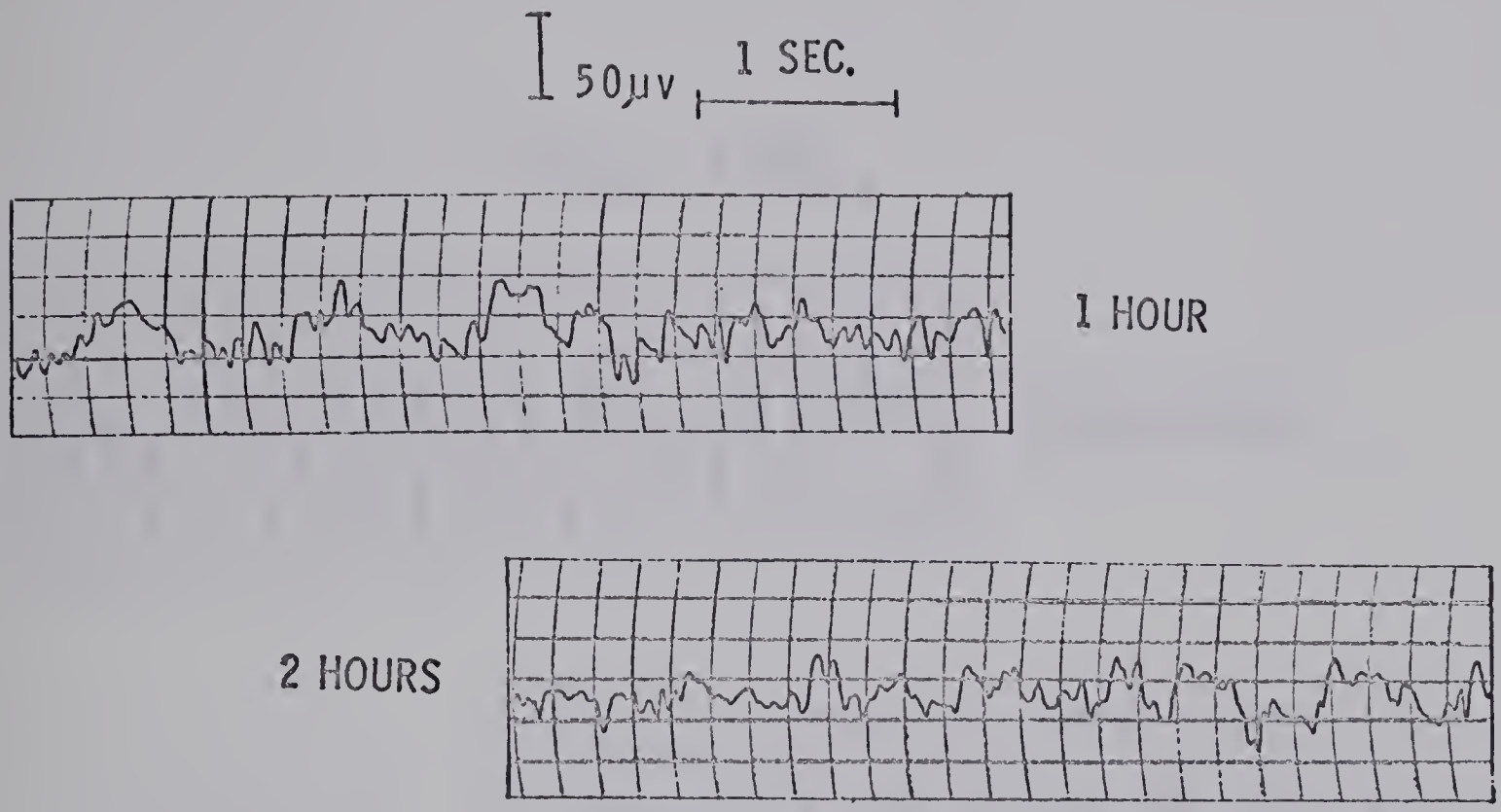


Figure 17

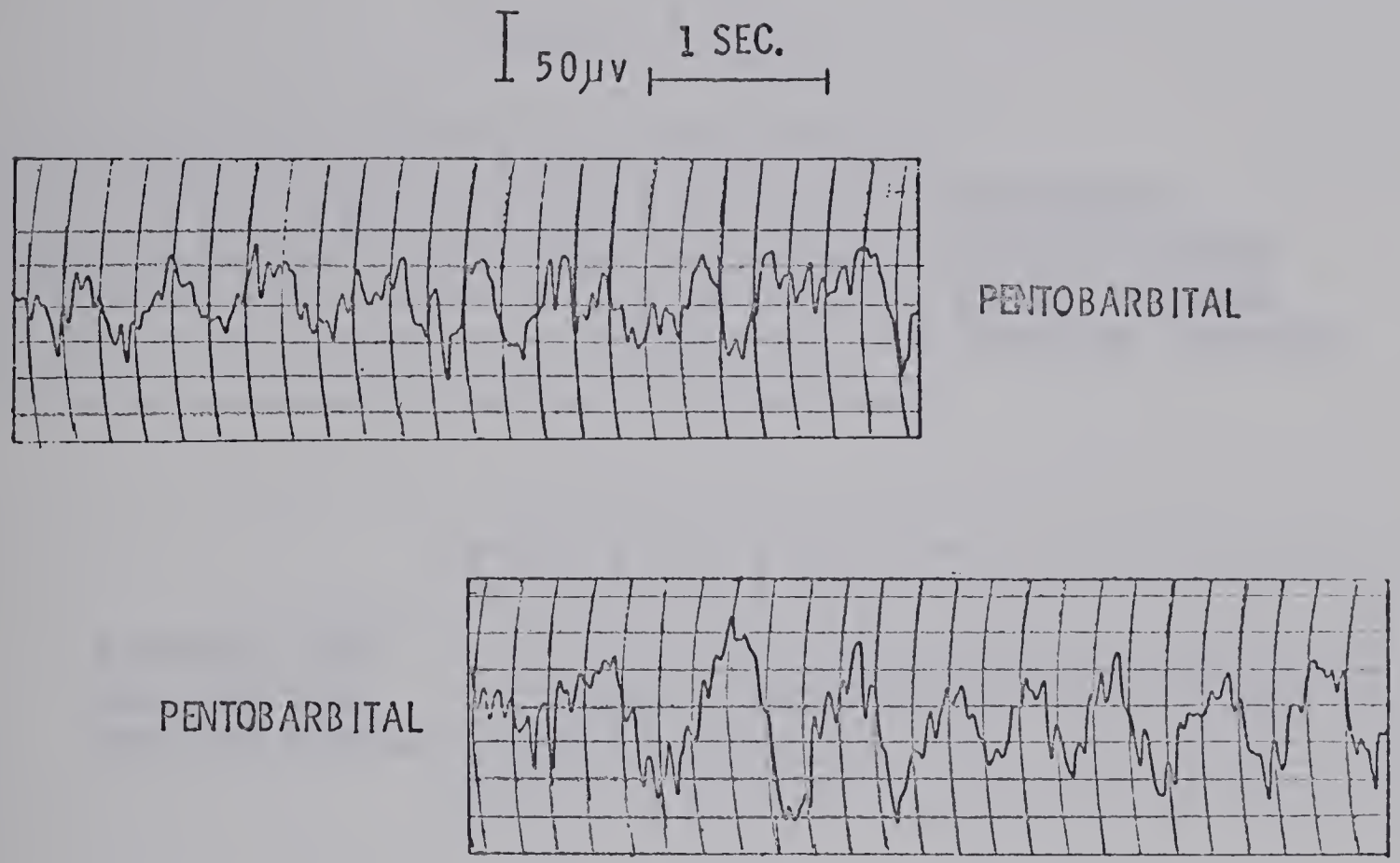

50μv
1 SEC.
PENTOBARBITAL
PENTOBARBITAL
PREHEMORRHAGE
IMMEDIATELY
AFTER HEMORRHAGE
HIGH CSF PRESSURE
LOW PERFUSION PRESSURE

Figure 18a

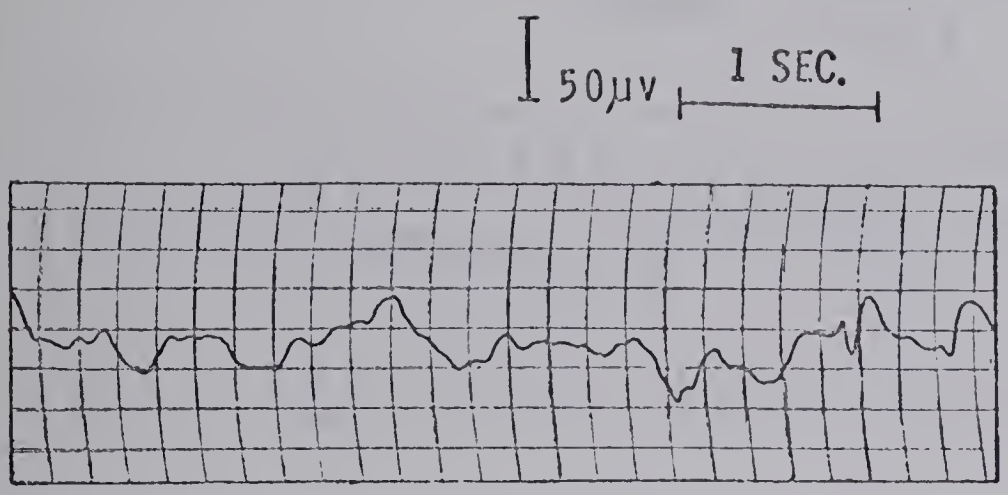

50μv
1 SEC.
60 SECONDS
POST HEMORRHAGE
SLIGHT REDUCTION
PERFUSION PRESSURE
2 MINUTES AFTER
SAH PERFUSION
PRESSURE NORMAL
15 MINUTES
NORMAL PERFUSION
PRESSURE
30 MINUTES

Figure 18b

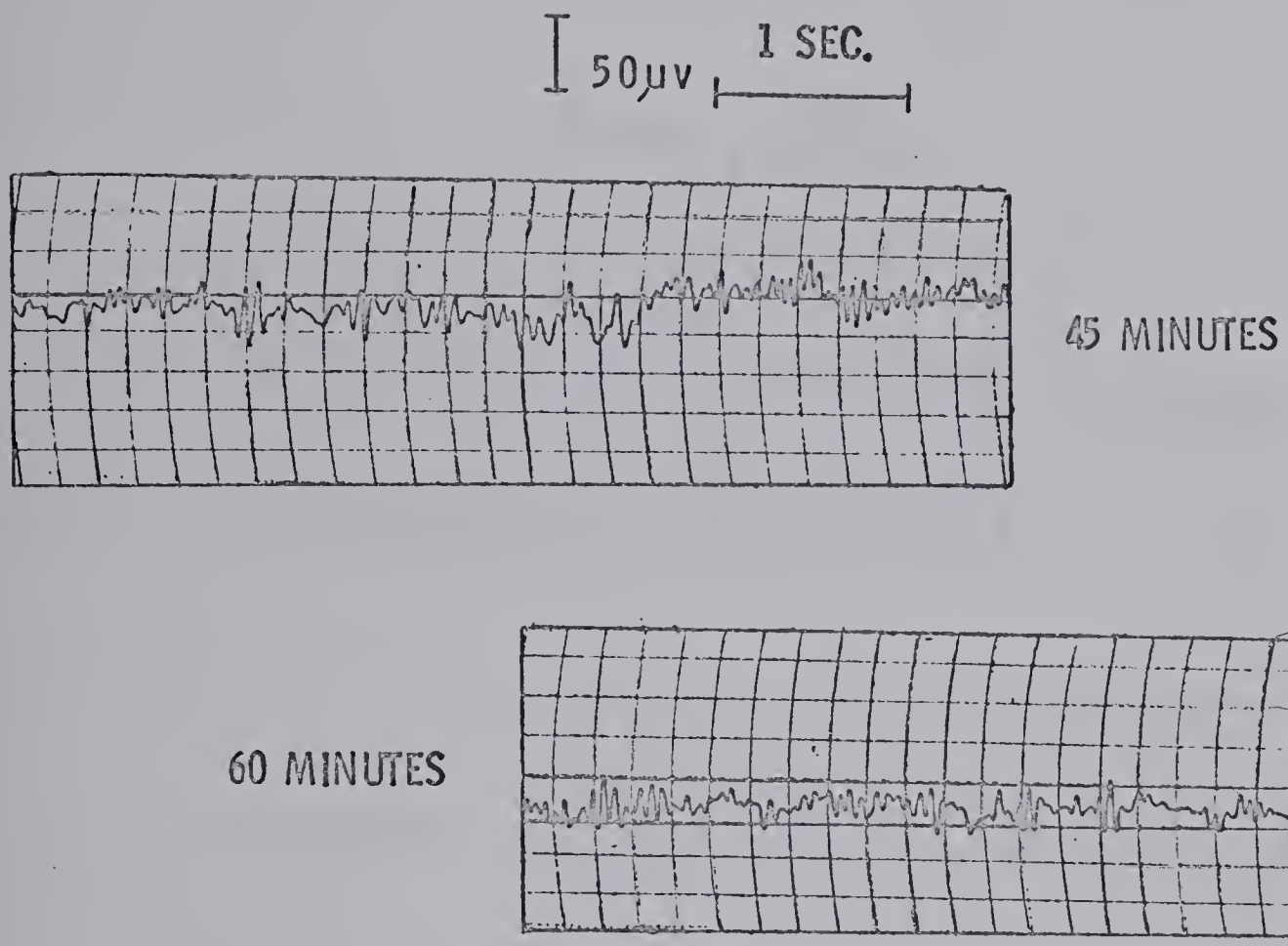


Figure 18c

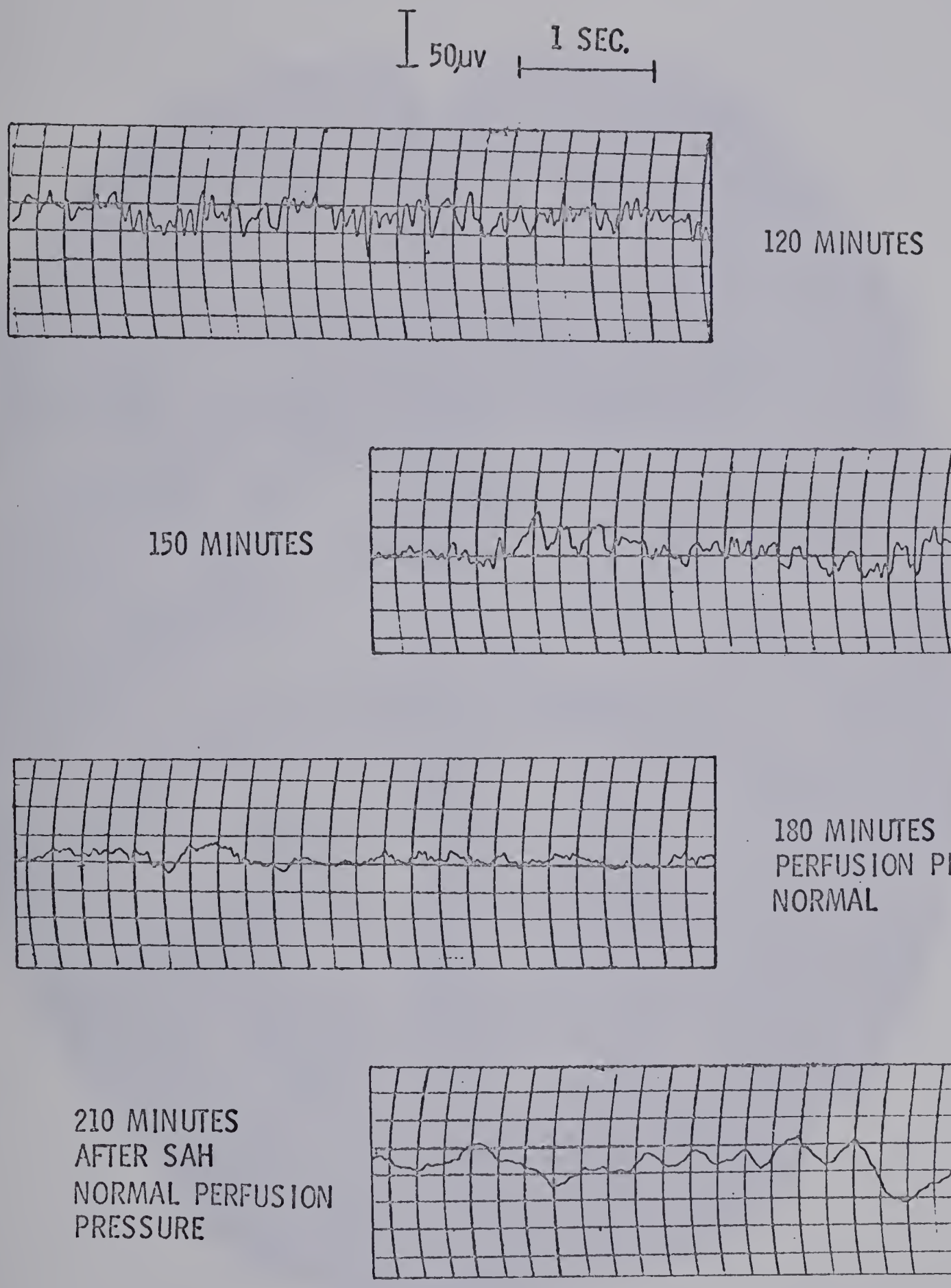

50μv
1 SEC.
120 MINUTES
150 MINUTES
180 MINUTES
PERFUSION PRESSURE
NORMAL
210 MINUTES
AFTER SAH
NORMAL PERFUSION
PRESSURE

Figure 18d

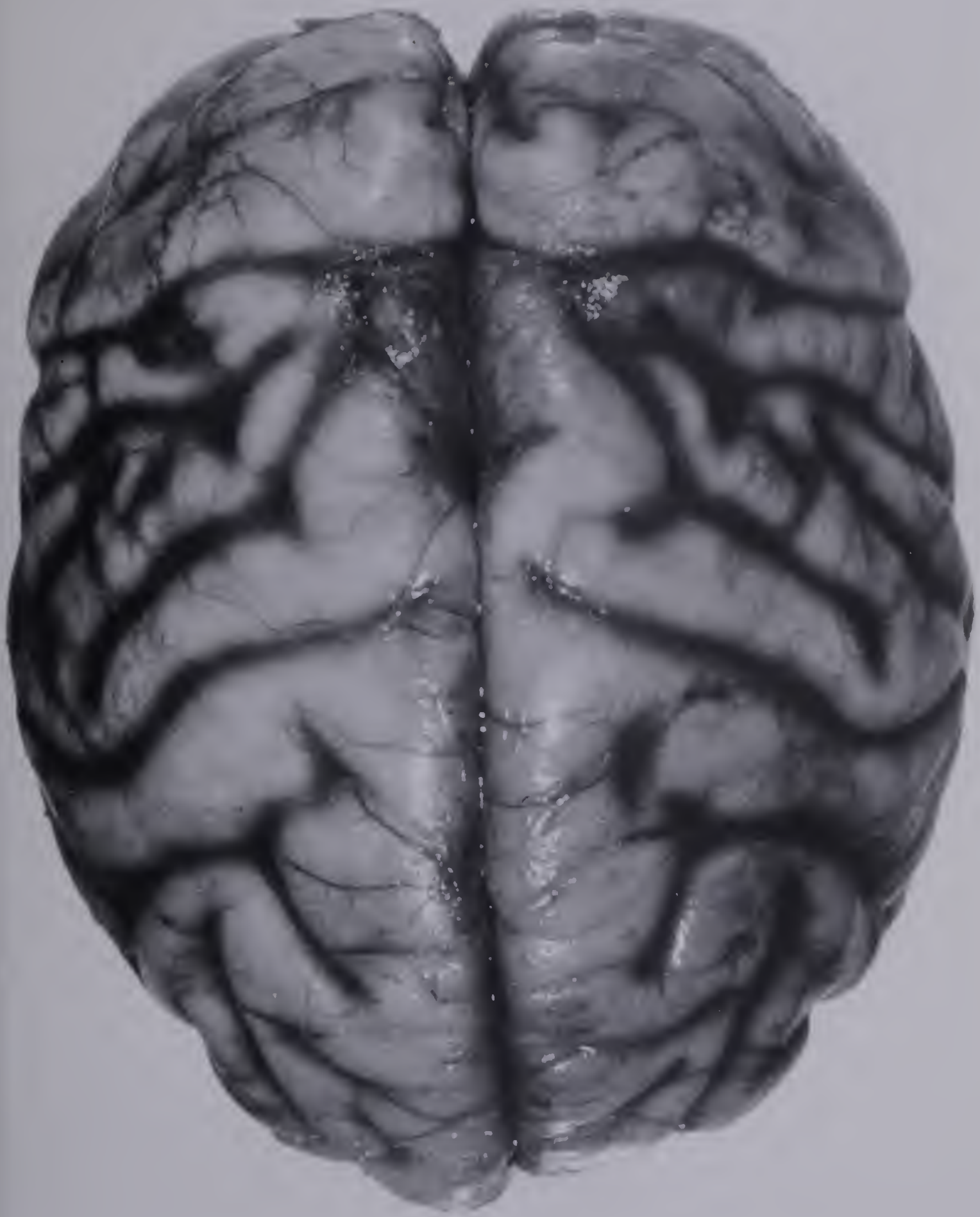


Figure 19

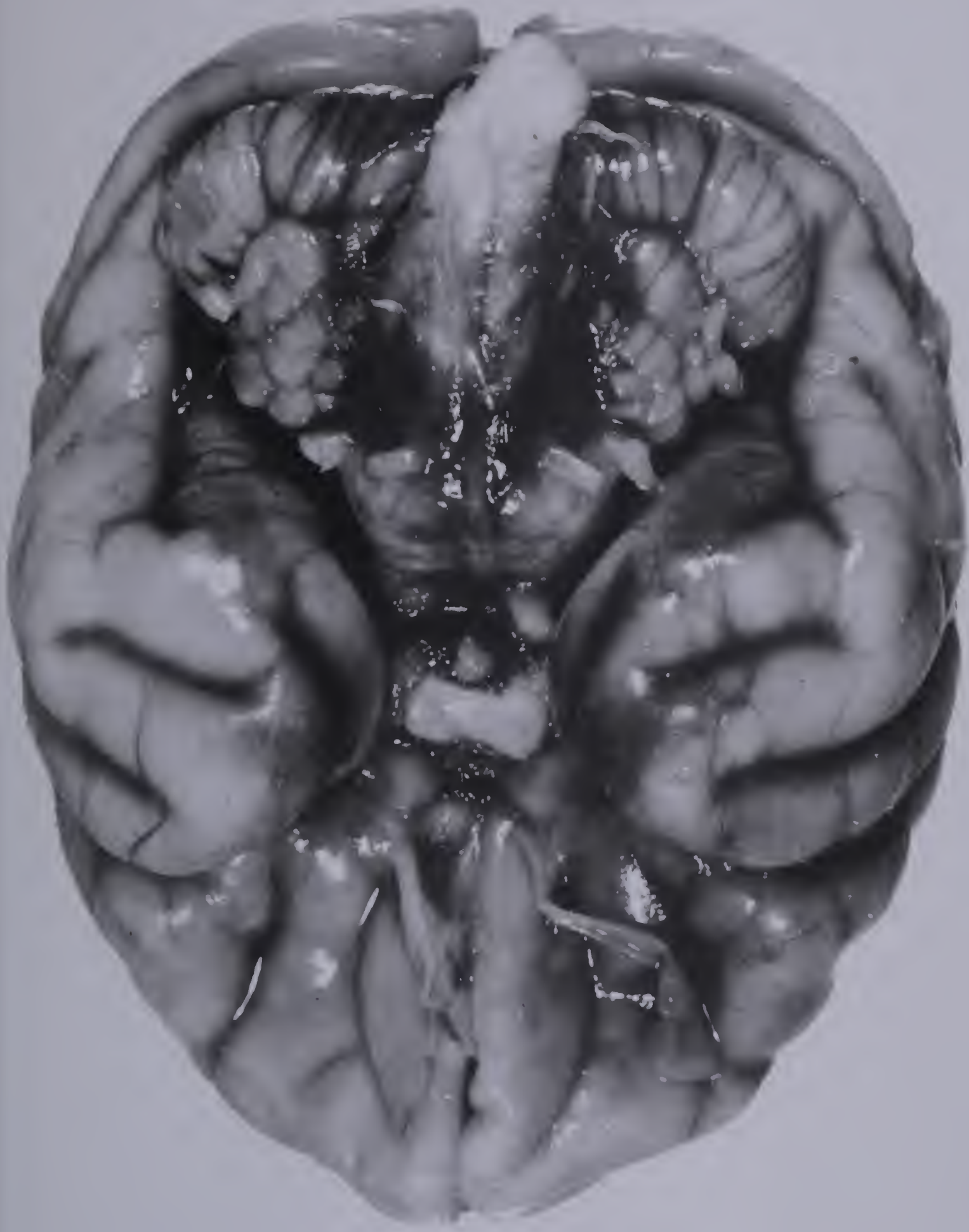


Figure 20

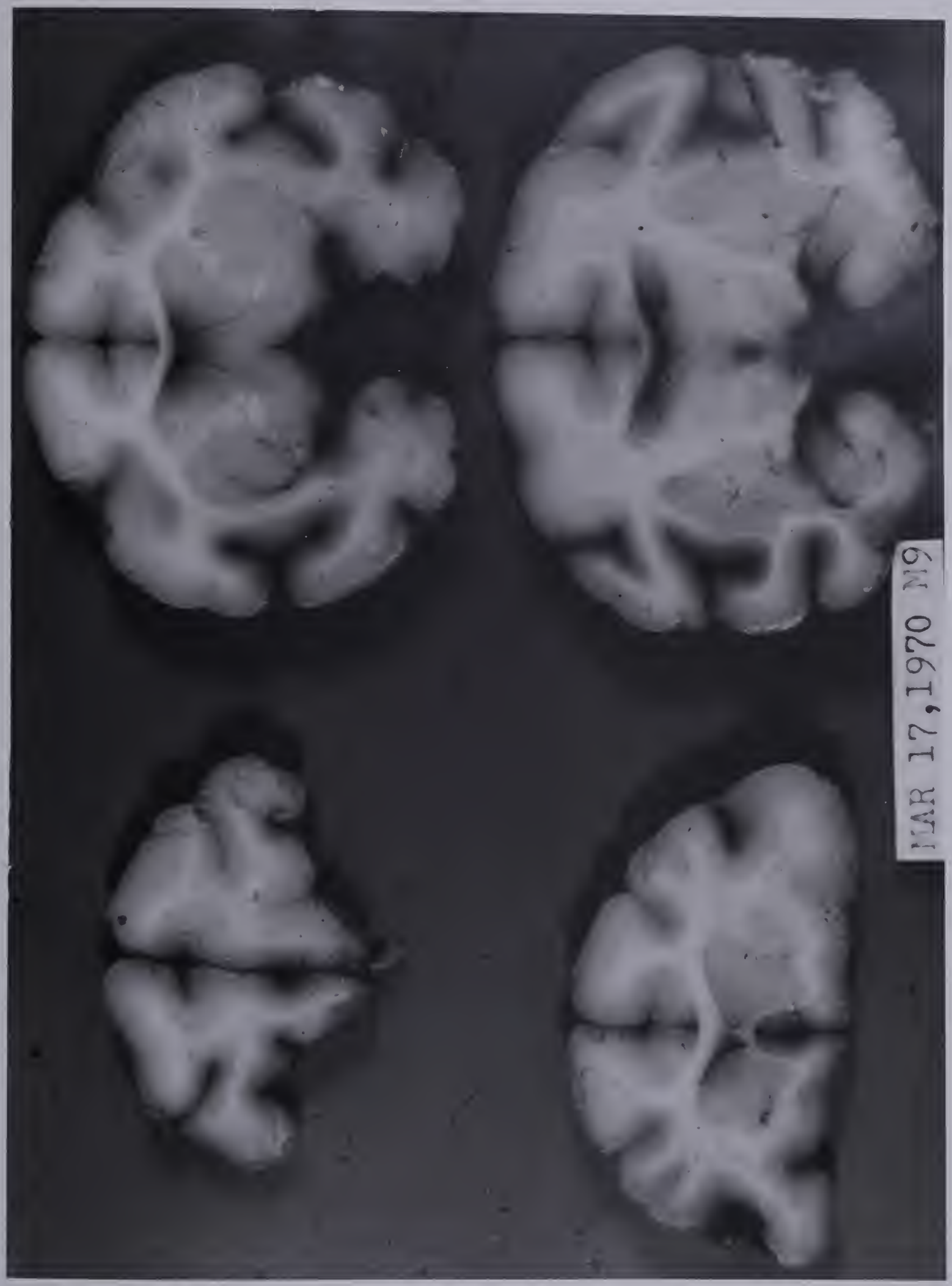


Figure 21

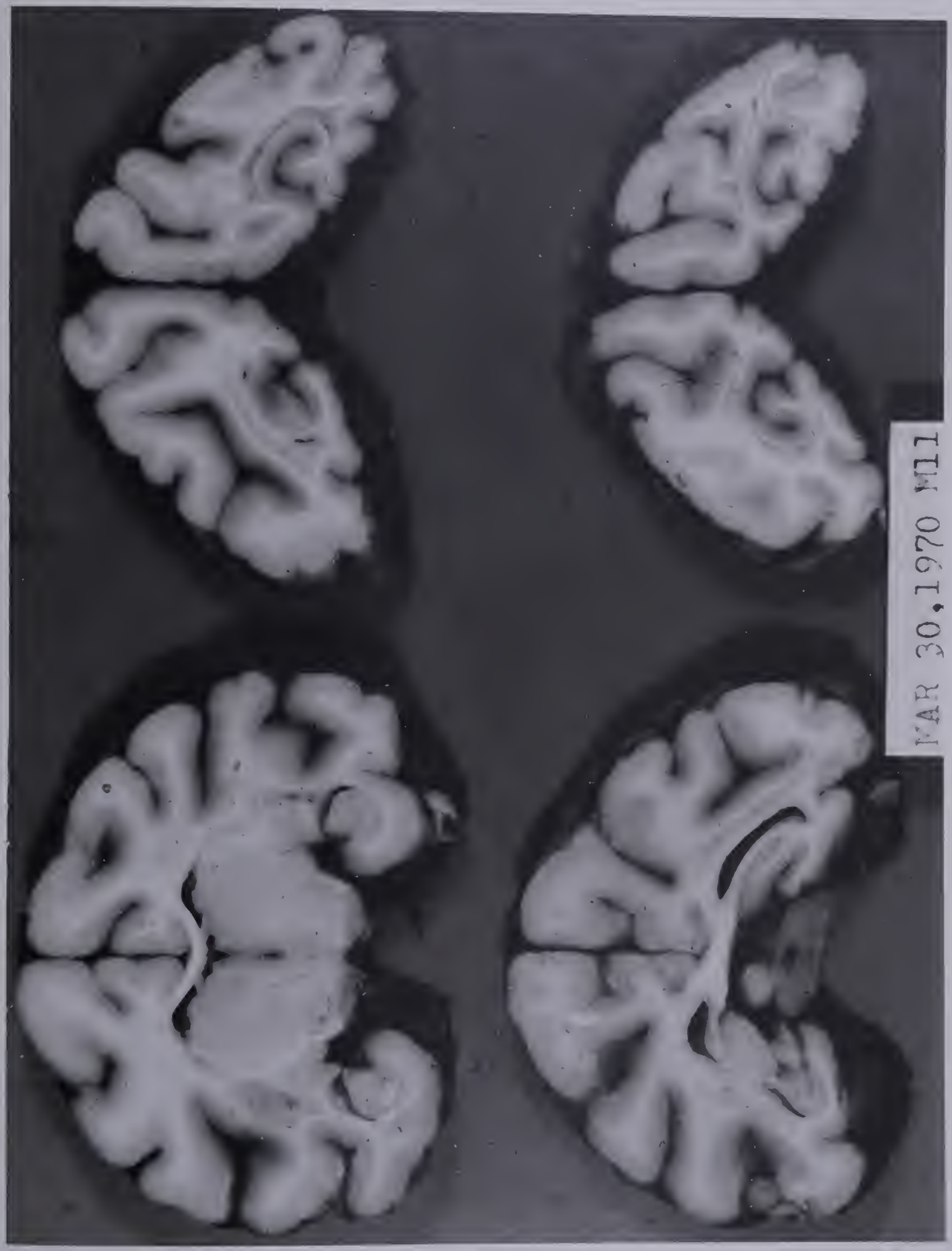


Figure 22

CHAPTER V

DISCUSSION

5.1 Comments on Methodology

The methodology involved in the determination of cerebral blood flow from the washout of freely diffusible radioisotope is well established. (23, 24, 28,44,53,56). A quantitative estimation of cerebral blood flow is obtained by this method providing extracranial circulation is excluded.

In this particular study the extracranial circulation was not excluded and the effect of this component upon the final cerebral blood flow values was evident in the lack of correlation between values obtained by the three methods described.

Examination of the curve frequently revealed a distribution of values that could not be resolved into two components; often three or four components were found (Figure 23). In experiments in which the carotid cannula was threaded into the internal carotid artery reflux into the extracranial circulation was evident on the angiograms performed in the initial experiments before angiography was abandoned. Therefore, reflux of the radioisotope into the extracranial circulation must be assumed in some but not all of the flow determinations.

Determination of cerebral blood flow by Zierler's height-over-area method is dependent on the input function*. The relationship between flow and the transit time of an indicator is established by an instantaneous injection of the indicator (a delta injection). If the injection is not instantaneous the effect is to decrease the maximum height of the concentration curve and also produce an increase in the area under the curve.

---

* The time vs quantity curve of the injected tracer

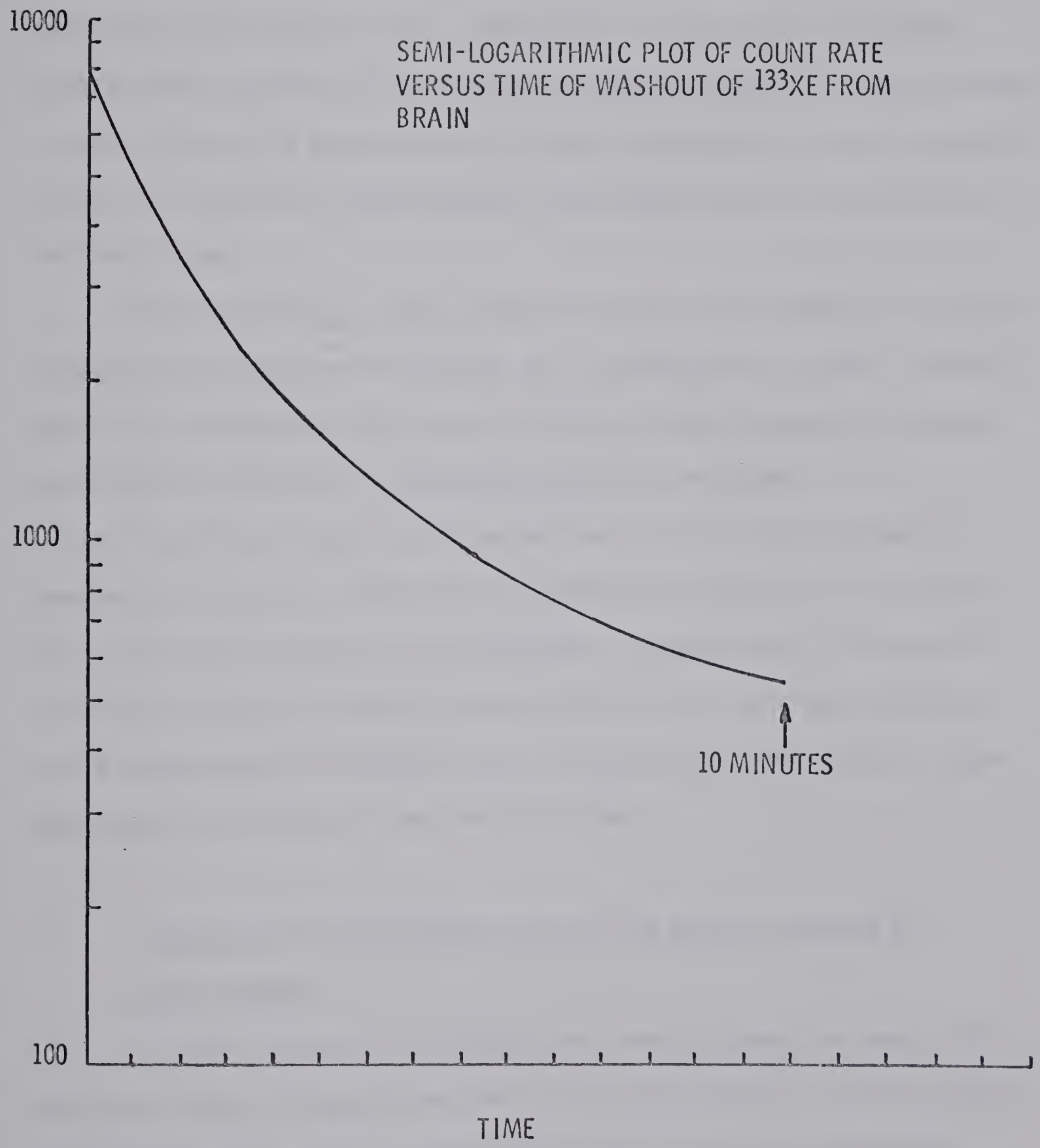

10000
1000
100
SEMI-LOGARITHMIC PLOT OF COUNT RATE VERSUS TIME OF WASHOUT OF 133XE FROM BRAIN
10 MINUTES
TIME

Figure 23

Hutten et al (27) have shown that, with injection times of one second and seven seconds, there is a 20% underestimation of flow with the longer injection. The longer the duration of injection the greater the underestimation of flow. Values obtained by the initial slope method are not affected by the injection time. Therefore, in experiments involving repeated determinations of blood flow in a single subject the slope method is least affected by experimental variables and serves as a good index of increase or decrease in flow although this method tends to overestimate the true values.

Theoretically the slope method is based on the assumption that no concentration gradients are present in a non-homogenous tissue. However Lassen (41) and Hutten (27) have found that a bolus injection technique gives similar results to a prolonged injection technique.

The effect of recirculation has been investigated by Hoedt - Rasmussen et al (24). The error involved with recirculation is minimal and a correction for this is not required. In particular, the initial part of the clearance curve is least affected by any of the systematic errors encountered in cerebral blood flow determination. This includes extracranial contamination and recirculation.

5.2 Correlation of the Cerebral Blood Flow Values Obtained by Three Methods

In this study poor correlation was found between the mean cerebral blood flow calculated from the initial slope and the cortical blood flow calculated from the biological half life of the fast component. Hoedt - Rasmussen et. al (25) were able to show a good correlation between the initial slope result and cortical blood flow. Paulson et. al. (53)

and Wilkinson et. al. (70) found a rough correlation between cortical blood flow and the initial slope value. These two groups found a good correlation between mean cerebral blood flow determined by the height-over-area method and the initial slope method. In this study there was a close parallel between the two methods, although occasionally the initial slope method exceeded the result from the height-over-area method by greater than ten percent. This probably reflects the increase in the area under the curve arising from extracranial contamination. The values for mean cerebral blood flow calculated from the compartmental analysis according to Lassen (41) also paralleled the values calculated by the height-over-area and initial slope methods but were significantly lower. This reflects a poor fit of the curve into two components with a marked underweighting for the fast compartment. Evidence for this is demonstrated by the mean flow value calculated from the initial slope exceeding the cortical flow value. In further studies in which extracranial branches were tied, a close correlation of values of flow determined by the three methods was found in normal animals.

Lassen (25) and others (53) utilizing a multiprobe system have found similar values for cerebral blood flow in all probes excepting that viewing the temporal lobe where a slightly lower value is found. The initial slope method when utilized with a multiprobe system is accurate for studying the pathophysiology of the cerebral circulation. With this system significant alteration occurs between normal and pathological areas. Using one detector alone we could not successfully quantitate cerebral blood flow in the normal animal, a wide range of values being found even when pCO_2 and blood pressure remained constant. However, when cerebral blood flow was reduced it tended to remain low without wide fluctuations in values.

5.3 Cerebral Blood Flow and Subarachnoid Hemorrhage

In all experiments the values for cerebral blood flow at the beginning of each experiment were low which, in part, reflects the effect of barbiturates anesthesia. Pierce et. al. (54) showed that the administration of thiopentone reduced cerebral blood flow by 48% and cerebral oxygen uptake by 55%. Gleichman (1962) showed that a gross correlation exists between the oxygen uptake of the cerebral cortex and the depth of anesthesia as assessed by the EEG. Pierce (54) showed that a reduction in cerebral oxygen uptake of 55% occurred with thiobarbitone. Wechsler (69) found a reduction of 36% with half the dose used in Pierce's study. Thus, cerebral blood flow probably decreases in a linear fashion with increasing depth of barbiturate anesthesia.

The above reports are consistent with our findings of an EEG pattern consistent with barbiturate anesthesia. Fast activity and cerebral blood flow increased in parallel over the first 60 to 90 minutes as the barbiturate effect disappeared. No studies are available on the effect of nitrous oxide in cerebral blood flows. Generally, it is held that light nitrous oxide anesthesia has no effect on the cerebral blood flow.

In this study cerebral blood flow was not found to change significantly following induced subarachnoid hemorrhage.

In a previous experiment (12) the effect of induced subarachnoid hemorrhage on the calibre of the cerebral arteries was studied by an angiographic technique and a significant decrease in the diameter of the major cerebral arteries was noted in a high percentage of animals.

Although angiography was not used in the present experiment it was assumed that vasoconstriction would occur in some animals in response to the subarachnoid injection of blood and in two animals there was a

decrease in cerebral blood flow. However, one of these decreases was associated with a decrease in perfusion pressure. The second flow after hemorrhage in this latter animal was significantly increased above control values which illustrates loss of autoregulation occurring after the hypoxic stimulus with injection of the blood. In the other experiment the decrease in cerebral blood flow was a sign of experimental failure! In other animals studied no significant change in cerebral blood flow occurred with induction of subarachnoid hemorrhage. However, reduction in cerebral blood flow was found to occur later in the experiment at a time when the vasoconstriction from the contact with blood would normally have disappeared (10). The increase in cerebral blood flow in two animals probably represents a posthypoxic hypermia following injection of the blood. Haggendal et. al. (20) have shown that increased blood flow occurs following release of raised intracranial pressure. This effect is related to dilitation of pial vessels (19) the mechanism of which is probably related to hypoxia.

Fujishima et. al. (17) and Zwetnow et. al. (75) have shown that an increase in hydrogen ion concentration occurs with decreasing perfusion pressure. In the present study the perfusion pressure was transiently altered returning to normal within 40 to 60 seconds. Whether cerebrospinal fluid acidosis occurred is not known. The increase in flow in the two animals is evidence that significant hypoxia occurred resulting in dilatation of arterioles and reactive hyperemia upon release of the lowered perfusion pressure. The failure of the flow to increase in the remaining animals may reflect vasoconstriction caused by the subarachnoid blood.

5.4 Comments upon the Experimental Model

The pathophysiology surrounding the actual rupture of a cerebral aneurysm is not known. The rate of bleeding is dependent on the size of the rupture. The mechanism of loss of consciousness is not known but in some cases is probably related to an acute elevation of the cerebrospinal fluid pressure. The quantity of hemorrhage is similarly unknown. The amount of blood used in this study was based upon the primary mortality rate as determined in previous studies; this was found to average 25% with 4 ml. of blood. The injection time of twenty seconds was chosen arbitrarily.

The model used in this experiment, to simulate subarachnoid hemorrhage in a patient with ruptured aneurysm, was successful as shown in pathological examination. The gross characteristics at autopsy closely simulated the pathological situation in patients succumbing from rupture of an aneurysm. Histologic examination of brains in previous studies however, failed to reveal microscopic infarction as described by Smith (63) which may reflect a difference in species. A possible explanation is the failure to adequately simulate the clinical state following rupture of a cerebral aneurysm.

The mechanism of vasospasm is not known. Mechanical and chemical factors are felt to play a major role whereas neurogenic mechanisms are thought to play a small role. James et. al (30) in studies on baboons found no change in blood flow upon stimulation of the vagus. Stimulation of the cut end of the cervical sympathetic nerve caused a reduction in cortical and white matter blood flow; the reduction being of greater magnitude at higher values of pCO_2. These results illustrate an influence of the sympathetic nervous system upon cerebrovascular resistance. Whether this influence is significant is not known.

The cardiac arrythmias and pulmonary edema observed in subarachnoid hemorrhage may be related to an intense sympathetic discharge from hypothalamic stimulation (51). Spasm of intracranial arteries has been demonstrated upon exposure of these vessels to norepinephrine (9, 34). It is not unreasonable to speculate that increase sympathetic tone might exist in subarachnoid hemorrhage. However, neurogenic stimulation is known to have only a small effect upon cerebrovascular mechanisms. This does not explain the local vasospasm of the vessel bearing the aneurysm but may, in part, be responsible for the diffuse spasm postulated by Smith as the mechanism of the diffuse widespread microinfarction. Support for these views is found in the studies of Stornelli and French (55) where analysis of cases showed spasm to exist only in the presence of an elevated blood pressure.

CHAPTER VI

SUMMARY

6.1 Cerebral blood flow was measured before and after the induction of subarachnoid hemorrhage in Rhesus monkeys which were lightly anesthetized with an oxygen nitrous-oxide mixture. Determination of cerebral blood flow was by the radioisotope method of Lassen and Ingvar using ^{133}Xe, in saline, injected into a cannula threaded into the internal carotid artery. A Fortran program was written to determine values for cerebral blood flow calculated by the methods of compartmental analysis, initial slope and the stochastic height over area methods. Blood pressure, CSF pressure, heart rate, EEG, ECG and blood gases were monitored.

6.2 Cerebral blood flow after subarachnoid hemorrhage was not found to differ significantly from control values in the same animal. This finding is postulated to be due to a balance between the spasmogenic effect of fresh autogenous blood and a metabollic acidosis secondary to hypoxia occurring at the time of hemorrhage. Arteriolar dilitation occurs with lowering of the perfusion pressure and, after release of the elevated cerebrospinal fluid pressure found during the injection, a posthypoxic hyperemia occurs. This was found in two experiments. The failure to find an elevation of cerebral blood flow after hemorrhage in the remaining experiments is possibly related to vasospasm. A significant reduction in cerebral blood flow was found in one animal. However, in the single instance in which this occurred there was a significant fall in perfusion pressure.

6.3 Loss of autoregulation to change in perfusion pressure was noted in most experiments; the flow passively following spontaneous changes in blood pressure. The blood pressure and arterial carbon dioxide tension were not specifically altered in this study.

6.4 The cerebral blood flow was found to correlate well with the frequency content of the EEG. This was true also at the beginning of each experiment before the effect of the barbiturate anesthesia had disappeared.

6.5 Cardiac arrythmias of supraventricular and ventricular origin were noted. Elevation of the ST segment, increased amplitude of the T wave and prolongation of the QT interval were also noted. These findings are similar to those found in patients with spontaneous subarachnoid hemorrhage.

6.6 There was a good correlation of mean cerebral blood flow calculated by the height-over-area and the initial slope methods. Values calculated from the initial slope exceeded those calculated by the height-over-area method by approximately 10%.

6.7 At higher cerebral blood flow levels the mean cerebral blood flow calculated by compartmental analysis underestimated the values calculated by the method of Zierler and by the initial slope method. This was thought to be due to an underestimate of the fast component by the curve fitting procedure and the use of a constant ratio of grey matter to white matter.

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APPENDIX A

Operating Methodology for the Hewlett Packard 2116 Laboratory Computer for Calculation of Cerebral Blood Flow and Sample Output.

Method of Utilizing the Hewlett Packard
Laboratory Computer - Example run

```
LOADING ADDRESS      077760

LOADER ENABLED

LOAD ADDRESS, PRESET , RUN

LOADER PROTECT

SWITCH 0 UP

PRESET, RUN

INPUT FR=FRESH; CO=CONTINUATION

CO
INPUT :DATE,XXXXXXXXXX,H,M

@:DATE,AUGUST6,
@
:JO
JOB        AUGUST6     TIME=0000 MIN. 03.2 SECS.
@
:RUN,WEST
0.3139      *(HEMATOCRIT=0.31,ARTERIAL CO2 TENSION=39MM/HG)
    A       B       C       D       X       Y     ERROR NERRS
  -.523    900   -.071    206   -.411   1043 .77E+05 10

   FG      FW      FT      FTC     A10    A10C     FI      FIC
 99.76   25.65   64.87   66.54   75.90   77.85   78.48   80.50

A=SLOPE OF FAST COMPONENT
B=INTERCEPT OF FAST COMPONENT
C=SLOPE OF SLOW COMPONENT
D=INTERCEPT OF SLOW COMPONENT
X=SLOPE OF THE INITIAL PART OF THE SEMILOGARITHMIC REPLOT
Y=INTERCEPT OF THE INITIAL SLOPE
ERROR=THE LEAST SQUARED ERROR INVOLVED IN FITTING THE SEMILOG-
      ARITHMIC REPLOT OF THE COUNT RATE TO A BI-EXPONENTIAL MODEL.
NERRS=THE NUMBER OF SPURIOUS CHANNELS THAT EXCEEDS THREE(3)
      STANDARD DEVIATIONS OF THE PRECEEDING AND FOLLOWING CHANNELS.
FG=FLOW IN THE FAST COMPARTMENT IN ML/100GM/MINUTE
FW=FLOW IN THE WHITE MATTER OR SLOW COMPARTMENT IN ML/100GM/MINUTE.
FT=MEAN CEREBRAL BLOOD FLOW CALCULATED FROM FG. AND FW. ACCORDING
   TO THE CONTRIBUTION OF EACH COMPARTMENT AS DETERMINED FROM
   THE INTERCEPTS
FTC=FT CORRECTED TO A CARBON DIOXIDE TENSION OF 40MM/HG
A10=MEAN CEREBRAL BLOOD FLOW IN ML/100GM/MIN AS CALCULATED FROM
    THE HEIGHT OVER AREA METHOD.
A10C=A10 NORMALIZED TO A CARBON DIOXIDE TENSION OF 40MM/HG
FI=MEAN CEREBRAL BLOOD FLOW CALCULATED FROM THE INITIAL SLOPE
FIC=FI NORMALIZED TO CO2 TENSION OF 40MM/HG
```

APPENDIX B

Analysis of cerebral blood flow by:

1. Stochastic analysis
2. Compartmental Analysis
3. Initial Slope

APPENDIX B

THE ANALYSIS OF CEREBRAL BLOOD FLOW

B.1 Stochastic Analysis

If a quantity of indicator is introduced instantaneously into a system of blood flow channels with a single entrance and a single exit, the transit time of the indicator is normally distributed, some of the indicator traversing the system rapidly and some slowly. If a quantity q of indicator is injected and the concentration C of the indicator at the exit is determined, the amount of indicator traversing the system in time t+dt is the product of the flow F, the concentration C(t), and the time dt:

$$q(t) = F \cdot C(t) \cdot dt \qquad \text{B.1.1}$$

As all the indicator will eventually traverse the whole system, it follows that the amount leaving is equal to the quantity injected.

Thus, $$q = F \cdot \int_0^\infty C(t)dt \qquad \text{B.1.2}$$

assuming the flow is constant.

Now the quantity of indicator leaving the system per unit time is $F \cdot C(t)$ the fraction h(t) that has left the system in unit time is given by

$$h(t) = \frac{F \cdot C(t)}{q} \qquad \text{B.1.3}$$

As all the indicator will eventually leave the system,

$$\int_0^\infty h(t)dt = 1 \qquad \text{B.1.4}$$

The volume of the system (V) is related to that volume of indicator with a traversal time in the neighborhood of t: i.e., t+dt. The system volume is then the sum of all these elements dV to infinite time.

The fraction of indicator with a traversal time dt is equal to h(t)dt, and the rate at which this fraction leaves the system is F·h(t). This volume of indicator is equal to the rate of output multiplied by the time required for output:

$$V = F \int_0^\infty t \cdot h(t)dt \qquad \text{B.1.5}$$

Since h(t) is the traversal time frequency, then $\int_0^\infty t \cdot h(t)$ is the mean $\bar{t}$ of the traversal times, therefore:

$$\bar{t} = V/F \qquad \text{B.1.6}$$

Recalling that the fraction of indicator traversing the system between t and t+dt is h(t)dt and that $\int_0^\infty h(t)dt = 1$, it follows that the amount of indicator traversing the system in time t is $\int_0^t h(t)dt = H(t)$ which is the cumulative traversal time frequency function, i.e., the cumulative fraction of indicator that has left the system in time t. Therefore, the fraction of the original amount of indicator injected that has left the system at time t is H(t)·q. What is detected by external counting of the radioactive indicator is some measure of q(t).

Examining the area under the curve of q(t) we find:

$$\int_0^\infty q(t)dt = q(0) \int_0^\infty (1-H(t))dt \qquad \text{B.1.7}$$

Meier and Zierler (48) have shown that $\int_0^\infty (1-H(t))dt$ is the mean $\bar{t}$ of the traversal times. From equation (6), $\bar{t} = V/F$; therefore:

$$\frac{1}{q(0)} \cdot \int_0^\infty q(t)dt = \bar{t} = V/F$$

and

$$F/V = \frac{q(0)}{\int_0^\infty q(t)dt} = \frac{\text{peak or zero value}}{\text{area}} \qquad \text{B.1.8}$$

The same workers have shown that with a constant injection the same relationship $\bar{t}$ - V/F holds. With V as the volume obtained when tracer is introduced at a constant rate, and is allowed to distribute itself at a steady state concentration, a relation between V and V_i, the volume of

tissue, can be established in the following way. If an amount q of indicator is introduced and allowed to distribute itself at steady state concentration and if $C = q/V$ and $C_i = q/V_i$, then $(q/V_i)/(q/V) = V/V_i = \lambda$, the partition coefficient, or ratio of indicator concentration between blood and tissue. Hence, as $V = V_i \cdot \lambda$,

$$\frac{F}{V_i} \cdot \lambda = \frac{q(0)}{\int_0^\infty q(t)dt} \qquad \text{B.1.9}$$

It has been shown that an index of cerebral blood flow can be obtained from the curve described by a ten minute washout period, and a true value by extrapolation of the tail of the curve to infinity (24).

B.2 Compartmental Analysis

Kety (37) applied the Fick principle to the study of cerebral blood flow. He showed that the rate of change of the quantity of an indicator in a homogeneous tissue is described by the flow through the system multiplied by the difference in the concentration of indicator in arterial and venous blood.

Thus, $$\frac{dq}{dt} = F(C_a - C_v). \qquad \text{B.2.1}$$

This relationship holds for constant flow and homogeneous tissue. Dividing both sides by V, the volume of distribution of tracer, and using $q/V = C$, gives

$$dC/dt = (F/V)(C_a - C_v). \qquad \text{B.2.2}$$

As shown previously, the ratio of the concentration of tracer between blood and tissue is constant. Hence the relationship:

$$dC/dt = (F/V_i \cdot \lambda) \cdot (C_a - C_v) \qquad \text{B.2.3}$$

If the tissue is homogeneous, then the tracer washout is described by $C(t) = C(0) \exp(-F \cdot t/V \cdot \lambda)$, as the concentration in arterial blood is zero at the beginning of washout.

With reference to cerebral blood flow, Lassen et. al. (41) have assumed that the brain can be described by two compartments in parallel. In an inhomogeneous organ such as the brain, the relationship bewteen average flow and average concentration is:

$$\bar{C} = \frac{\Sigma w_i C_i(0)\ \exp(-F_i \cdot t/\lambda_i)}{\Sigma w_i} \qquad \text{B.2.4}$$

For a two compartment system the relationship is:

$$\bar{C} = w_g \cdot F_g \cdot D \cdot \ \exp(-F_g \cdot t/\lambda_g) \ + w_w \cdot F_w \cdot D \cdot \exp(-F_w \cdot t/\lambda_w) \qquad \text{B.2.5}$$

where D is a relative measure of the quantity of tracer injected, w_g and w_w are the relative weights of the gray and white matter, and F_g and F_w are the flow in the gray and white matter. Further, $w_g \cdot F_g \cdot D = I_g$, where I_g is the intercept value of the count rate of the fast component. Hence,

$$\bar{C} = I_g \cdot \exp(-k_g \cdot t) + I_w \exp(-k_w \cdot t).$$

$$w_g = (I_g/f_g)/(I_g/f_g + I_w f_w).$$

$$w_w = 1 - w_g.$$

$$\bar{F} = F_g \cdot w_g + F_w \cdot w_w. \qquad \text{B.2.6}$$

The semi-logarithmic replot of count rate versus time of the decay curve can be described by two exponential functions. The flow in each compartment is calculated from the half-time of each component according to

$$F_g = \lambda_g \cdot \frac{0.693}{T_{\frac{1}{2}\,g}}$$

$$F_w = \lambda_w \cdot \frac{0.693}{T_{\frac{1}{2}\,w}} \qquad \text{B.2.7}$$

B.3 Initial Slope

If in an inhomogeneous tissue the concentration in all compartments is equal, then

$$\bar{C} = C(0) \cdot \frac{\Sigma^{W}i \exp(-F_i \cdot t/\lambda i)}{\Sigma^{W}i}$$

$$\bar{C}/C(0) = \frac{\Sigma^{W}_i \exp(-F_i \cdot t/\lambda i)}{W_i} \qquad \text{B.3.1}$$

The initial slope of this composite curve is $\bar{F}/\lambda$, thus $\frac{\Sigma^{W}i \cdot F_i}{\Sigma^{W}i} = \bar{F}$

i.e. the average blood flow. The slope of the initial part of the curve can be conveniently obtained from the semi-logarithmic replot of the count rate vs. time. The initial part of the semi-logarithmic replot is a straight line and the slope in 'percentage of a decade' is readily calculated. Although this method is not as accurate as the other methods described above it is a useful index when one is studying repeated determination in one subject and flow is not constant for a long enough period for the determination of a 10-minute curve.

APPENDIX C

FLOW CHART

FORTRAN PROGRAM

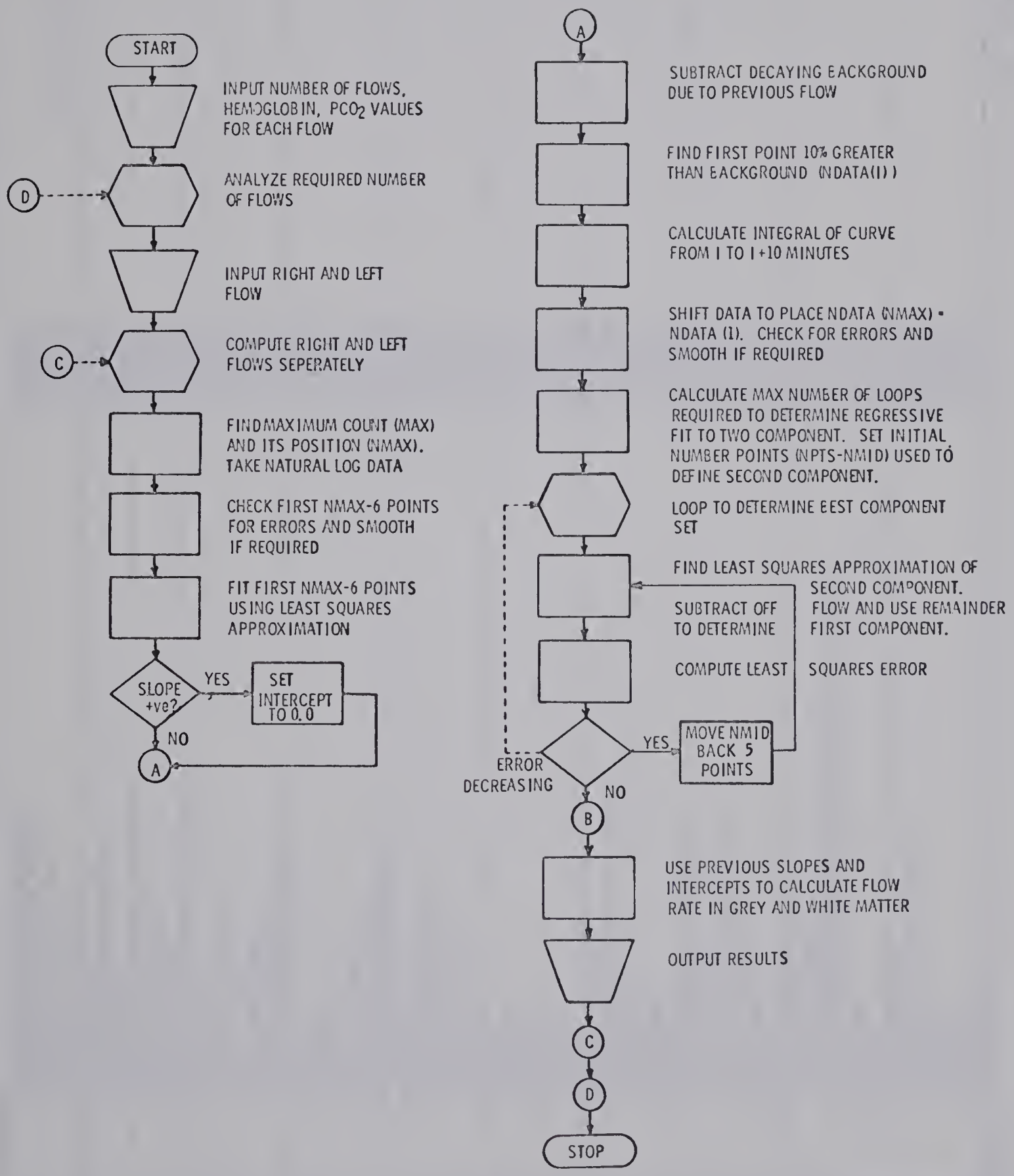
for Calculation of Cerebral Blood Flow

and

EXAMPLE OF OUTPUT

from IBM 360/67

Computer


START
INPUT NUMBER OF FLOWS, HEMOGLOBIN, PCO_2 VALUES FOR EACH FLOW
D
ANALYZE REQUIRED NUMBER OF FLOWS
INPUT RIGHT AND LEFT FLOW
C
COMPUTE RIGHT AND LEFT FLOWS SEPERATELY
FIND MAXIMUM COUNT (MAX) AND ITS POSITION (NMAX). TAKE NATURAL LOG DATA
CHECK FIRST NMAX-6 POINTS FOR ERRORS AND SMOOTH IF REQUIRED
FIT FIRST NMAX-6 POINTS USING LEAST SQUARES APPROXIMATION
SLOPE +ve?
YES
SET INTERCEPT TO 0.0
NO
A
A
SUBTRACT DECAYING BACKGROUND DUE TO PREVIOUS FLOW
FIND FIRST POINT 10% GREATER THAN BACKGROUND (NDATA(I))
CALCULATE INTEGRAL OF CURVE FROM I TO I+10 MINUTES
SHIFT DATA TO PLACE NDATA (NMAX) - NDATA (I). CHECK FOR ERRORS AND SMOOTH IF REQUIRED
CALCULATE MAX NUMBER OF LOOPS REQUIRED TO DETERMINE REGRESSIVE FIT TO TWO COMPONENT. SET INITIAL NUMBER POINTS (NPTS-NMID) USED TO DEFINE SECOND COMPONENT.
LOOP TO DETERMINE BEST COMPONENT SET
FIND LEAST SQUARES APPROXIMATION OF SECOND COMPONENT.
SUBTRACT OFF SECOND COMPONENT. FLOW AND USE REMAINDER TO DETERMINE FIRST COMPONENT.
COMPUTE LEAST SQUARES ERROR
ERROR DECREASING
YES
MOVE NMID BACK 5 POINTS
NO
B
USE PREVIOUS SLOPES AND INTERCEPTS TO CALCULATE FLOW RATE IN GREY AND WHITE MATTER
OUTPUT RESULTS
C
D
STOP

1, 12 x 11 MATT.

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```
$LIST FLOWSOURCE
      1            COMMON DATA(200),NDATA(200)                              FLOW0001
      2            DIMENSION NDAT(401),KCO(25)                              FLOW0002
      3            DATA NR/'  '/,SR/' *'/                                   FLOW0003
      4            TINT=10.0/150.0                                          FLOW0004
      5            WRITE(6,600)                                             FLOW0005
      6            READ(1,300)NMONK,NTOT,HT                                 FLOW0006
      7            WRITE(6,700)                                             FLOW0007
      8            READ(1,100)(KCO(I),I=1,NTOT)                             FLOW0008
      9            WRITE(8,400)NMONK                                        FLOW0009
     10            DO 52 L=1,NTOT                                           FLOW0010
     11            READ(7,200)(NDAT(I),I=1,401)                             FLOW0011
     12            DO 50 K=1,2                                              FLOW0012
     13            IF(K.EQ.1) GO TO 4                                       FLOW0013
     14            J=1                                                      FLOW0014
     15            DO 2 N=202,401                                           FLOW0015
     16            NDATA(J)=NDAT(N)                                         FLOW0016
     17            DATA(J)=FLOAT(NDATA(J))                                  FLOW0017
     18            J=J+1                                                    FLOW0018
     19          2 CONTINUE                                                 FLOW0019
     20            GO TO 8                                                  FLOW0020
     21          4 DO 6 N=1,200                                             FLOW0021
     22            NDATA(N)=NDAT(N+1)                                       FLOW0022
     23            DATA(N)=FLOAT(NDATA(N))                                  FLOW0023
     24          6 CONTINUE                                                 FLOW0024
     25          8 RLG=107.5*HT+102.5                                       FLOW0025
     26            RLW=214.3/RLG                                            FLOW0026
     27            RLG=112.6/RLG                                            FLOW0027
     28            MAX=0                                                    FLOW0028
     29            NMAX=1                                                   FLOW0029
     30            ERR=1E20                                                 FLOW0030
     31            NERRS=0                                                  FLOW0031
     32            AREA=0.0                                                 FLOW0032
     33            S=0.0                                                    FLOW0033
     34            T=0.0                                                    FLOW0034
     35            DO 10 I=1,200                                            FLOW0035
     36            IF(NDATA(I).LE.MAX) GO TO 10                             FLOW0036
     37            MAX=NDATA(I)                                             FLOW0037
     38            NMAX=I                                                   FLOW0038
     39         10 CONTINUE                                                 FLOW0039
     40            NDF=NMAX-6                                               FLOW0040
     41            CALL CHECK(1,NDF,NERRS)                                  FLOW0041
     42            DO 12 I=1,NDF                                            FLOW0042
     43            IF(DATA(I).EQ.0.0) GO TO 16                              FLOW0043
     44            DATA(I)=ALOG(DATA(I))                                    FLOW0044
     45         12 CONTINUE                                                 FLOW0045
     46            CALL LSQ(1,NDF,S,T,TINT)                                 FLOW0046
     47            IF(S.GT.0.0) T=0.0                                       FLOW0047
     48            DO 14 I=1,200                                            FLOW0048
     49            DATA(I)=FLOAT(NDATA(I))-T*EXP(S*FLOAT(I-1)*TINT)         FLOW0049
     50            NDATA(I)=IFIX(DATA(I)+0.5)                               FLOW0050
     51         14 CONTINUE                                                 FLOW0051
     52         16 NP=NR                                                    FLOW0052
     53            NPTS=201-NMAX                                            FLOW0053
     54            IF(NPTS.LT.151) GO TO 18                                 FLOW0054
     55            NPTS=151                                                 FLOW0055
     56            GO TO 20                                                 FLOW0056
     57         18 NP=SR                                                    FLOW0057
     58         20 BKGND=0.0                                                FLOW0058
```

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```
      DO 22 I=1,NDF                                                     FLOW0059
      BKGND=BKGND+FLOAT(NDATA(I))                                       FLOW0060
   22 CONTINUE                                                          FLOW0061
      BKGND=BKGND/FLOAT(NDF)                                            FLOW0062
      DO 24 I=1,200                                                     FLOW0063
      IF((FLOAT(NDATA(I))).GT.(1.1*BKGND)) GO TO 26                     FLOW0064
   24 CONTINUE                                                          FLOW0065
   26 NF=I+NPTS-1                                                       FLOW0066
      DO 28 J=I,NF                                                      FLOW0067
      AREA=AREA+FLOAT(NDATA(J))*TINT                                    FLOW0068
   28 CONTINUE                                                          FLOW0069
      NT=(NPTS-26)/5                                                    FLOW0070
      NF=NMAX+NPTS-1                                                    FLOW0071
      CALL CHECK(NMAX,NF,NERRS)                                         FLOW0072
      DO 30 I=NMAX,NF                                                   FLOW0073
      NDATA(I-NMAX+1)=NDATA(I)                                          FLOW0074
      DATA(I-NMAX+1)=ALOG(DATA(I))                                      FLOW0075
   30 CONTINUE                                                          FLOW0076
      CALL LSQ(1,15,X,Y,TINT)                                           FLOW0077
      DO 42 J=1,NT                                                      FLOW0078
      NMID=NPTS-5*(J+5)                                                 FLOW0079
      DO 32 I=NMID,NPTS                                                 FLOW0080
      DATA(I)=ALOG(FLOAT(NDATA(I)))                                     FLOW0081
   32 CONTINUE                                                          FLOW0082
      CALL LSQ(NMID,NPTS,C1,D1,TINT)                                    FLOW0083
      DO 34 I=1,NPTS                                                    FLOW0084
      DATA(I)=FLOAT(NDATA(I))-D1*EXP(C1*FLOAT(I-1)*T)NT)                FLOW0085
      IF(DATA(I).LE.0.0) GO TO 36                                       FLOW0086
      DATA(I)=ALOG(DATA(I))                                             FLOW0087
   34 CONTINUE                                                          FLOW0088
      I=NPTS                                                            FLOW0089
      GO TO 38                                                          FLOW0090
   36 IF(I.EQ.1) GO TO 46                                               FLOW0091
      I=I-1                                                             FLOW0092
   38 CALL LSQ(1,I,A1,B1,TINT)                                          FLOW0093
      ERR1=0.0                                                          FLOW0094
      DO 40 I=1,NPTS                                                    FLOW0095
      ERR1=ERR1+(FLOAT(NDATA(I))-B1*EXP(A1*FLOAT(I-1)*TINT)             FLOW0096
     /-D1*EXP(C1*FLOAT(I-1)*TINT))**2                                   FLOW0097
   40 CONTINUE                                                          FLOW0098
      IF(ERR1.GT.ERR) GO TO 44                                          FLOW0099
      ERR=ERR1                                                          FLOW0100
      A=A1                                                              FLOW0101
      B=B1                                                              FLOW0102
      C=C1                                                              FLOW0103
      D=D1                                                              FLOW0104
   42 CONTINUE                                                          FLOW0105
      A=0.0                                                             FLOW0106
      B=0.0                                                             FLOW0107
   44 CBFG=69.315*RLG/(-0.69315/A)                                      FLOW0108
      CBFW=69.315*RLW/(-0.69315/C)                                      FLOW0109
      CBFT=(CBFG*(B+D))/(B+(D*RLG*(-0.69315/C))/(RLW*(-0.69315/A)))     FLOW0110
      GO TO 48                                                          FLOW0111
   46 A=0.0                                                             FLOW0112
      B=0.0                                                             FLOW0113
      CBFT=69.315*(0.52*RLG+0.48*RLW)/(-0.69315/C)                      FLOW0114
      CBFG=0.0                                                          FLOW0115
      CBFW=CBFT                                                         FLOW0116
   48 C10=100.0*(0.52*RLG+0.48*RLW)*FLOAT(NDATA(I)-NDATA(NPTS))/AREA    FLOW0117
      TMFI=-100.0*X*RLG                                                 FLOW0118
```

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```
      CBFC=1.0+0.025*FLOAT(KCO(L)-40)                                    FLOW0119
      C10C=C10/CBFC                                                      FLOW0120
      TMFIC=TMFI/CBFC                                                    FLOW0121
      CBFC=CBFT/CBFC                                                     FLOW0122
      A=0.4342945*A                                                      FLOW0123
      C=0.4342945*C                                                      FLOW0124
      X=0.4342945*X                                                      FLOW0125
      WRITE(8,500)L,A,B,C,D,X,Y,CBFG,CBFW,CBFT,CBFC,C10,C10C,TMFI,       FLOW0126
     /TMFIC,ERR,NERRS,NP                                                 FLOW0127
   50 CONTINUE                                                           FLOW0128
   52 CONTINUE                                                           FLOW0129
      STOP                                                               FLOW0130
  100 FORMAT(I2,24I3)                                                    FLOW0131
  200 FORMAT(I6,2(200I6))                                                FLOW0132
  300 FORMAT(I2,1X,I2,1X,F4.2)                                           FLOW0133
  400 FORMAT(1H1,'MONKEY',1X,I2,4X,'A',6X,'B',6X,'C',6X,'D',6X,          FLOW0134
     /'X',6X,'Y',6X,'FG',4X,'FW',3X,'CBFT',3X,'CBFC',2X,'CBF(10)',2X,    FLOW0135
     /'CBF(10)C',2X,'TMFI',3X,'TMFIC',2X,'LSQERR',1X,'NERRS'//)          FLOW0136
  500 FORMAT(1X,' FLOW ',1X,I2,1X,F6.3,1X,F6.0,1X,F6.3,1X,F6.0,          FLOW0137
     /1X,F6.3,1X,F6.0,1X,F6.2,1X,F5.2,1X,F6.2,1X,F6.2,1X,F6.2,3X,F6.2,   FLOW0138
     /3X,F6.2,1X,F6.2,1X,E8.3,1X,I2,A2)                                  FLOW0139
  600 FORMAT(1X,/'INPUT MONKEY NUMBER, NUMBER OF FLOWS, AND HEMOGLOBIN'/FLOW0140
     //'XX XX X.XX')                                                    FLOW0141
  700 FORMAT(1X,/'INPUT PCO2 VALUES'//' XX XX XX XX XX .............')   FLOW0142
      END                                                                FLOW0143
      SUBROUTINE LSQ(NS,NF,A,B,T)                                        FLOW0144
      COMMON DATA(200),NDATA(200)                                        FLOW0145
      SX=0.0                                                             FLOW0146
      SY=0.0                                                             FLOW0147
      SX2=0.0                                                            FLOW0148
      SXY=0.0                                                            FLOW0149
      NPTS=NF-NS+1                                                       FLOW0150
      DO 2 I=NS,NF                                                       FLOW0151
      SX=SX+T*FLOAT(I-1)                                                 FLOW0152
      SY=SY+DATA(I)                                                      FLOW0153
      SX2=SX2+(T*FLOAT(I-1))**2                                          FLOW0154
      SXY=SXY+DATA(I)*T*FLOAT(I-1)                                       FLOW0155
    2 CONTINUE                                                           FLOW0156
      A=(FLOAT(NPTS)*SXY-SX*SY)/(FLOAT(NPTS)*SX2-SX**2)                  FLOW0157
      B=EXP((SY-A*SX)/FLOAT(NPTS))                                       FLOW0158
      RETURN                                                             FLOW0159
      END                                                                FLOW0160
      SUBROUTINE CHECK(NS,NF,K)                                          FLOW0161
      COMMON DATA(200),NDATA(200)                                        FLOW0162
      IS=NS+1                                                            FLOW0163
      IF=NF-1                                                            FLOW0164
      DO 4 I=IS,IF                                                       FLOW0165
      IF(DATA(I-1).LT.0.0) DATA(I-1)=0.0                                 FLOW0166
      IF(DATA(I+1).LT.0.0) DATA(I+1)=0.0                                 FLOW0167
      IF(DATA(I).GT.(DATA(I-1)+3.0*SQRT(DATA(I-1)))) GO TO 2             FLOW0168
      IF(DATA(I).LT.(DATA(I+1)-3.0*SQRT(DATA(I+1)))) GO TO 2             FLOW0169
      GO TO 4                                                            FLOW0170
    2 K=K+1                                                              FLOW0171
      DATA(I)=(DATA(I-1)+DATA(I+1))/2.0                                  FLOW0172
      NDATA(I)=IFIX(DATA(I)+0.5)                                         FLOW0173
    4 CONTINUE                                                           FLOW0174
      RETURN                                                             FLOW0175
      END                                                                FLOW0176
END OF FILE
```

```
 $run flows 7=*tape*
#EXECUTION BEGINS

 INPUT MONKEY NUMBER, NUMBER OF FLOWS, AND HEMOGLOBIN

 XX XX X.XX
 14 07 0.30

 INPUT PCO2 VALUES

 XX XX XX XX XX .............
 40 40 40 39 36 40 39
```

MONKEY 14	A	B	C	D	X	Y	FG	FW	CBFT	CBFC	CBF(10)	CBF(10)C	TMFI	TMFIC	LSQERR	NERRS
FLOW 1	-0.483	3283.	-0.067	712.	-0.534	5078.	92.99	24.65	62.24	62.24	96.85	96.85	102.78	102.78	.476E 07	5
FLOW 1	-0.347	1457.	-0.039	275.	-0.543	2680.	66.74	14.43	42.37	42.37	91.17	91.17	104.40	104.40	.342E 07	5
FLOW 2	-0.351	2077.	-0.050	362.	-0.576	3944.	67.49	18.38	48.34	48.34	99.06	99.06	110.91	110.91	.873E 07	2
FLOW 2	-0.421	1156.	-0.043	250.	-0.554	2014.	81.03	15.74	46.65	46.65	89.45	89.45	106.67	106.67	.151E 07	4
FLOW 3	-0.407	1559.	-0.050	223.	-0.572	2674.	78.32	18.43	55.65	55.65	103.25	103.25	110.15	110.15	.286E 07	8
FLOW 3	-0.810	1163.	-0.060	219.	-0.570	1270.	155.95	22.14	79.62	79.62	97.70	97.70	109.66	109.66	.629E 05	9
FLOW 4	-0.775	721.	-0.043	152.	-0.634	941.	149.10	15.73	60.30	61.84	91.07	93.41	122.00	125.12	.824E 05	17
FLOW 4	-1.166	1616.	-0.055	165.	-0.599	1322.	224.31	20.28	116.19	119.17	106.53	109.27	115.25	118.20	.352E 06	8
FLOW 5	-0.583	666.	-0.033	160.	-0.568	965.	112.20	12.17	43.27	48.07	72.00	80.00	109.30	121.44	.141E 06	4
FLOW 5	-0.641	600.	-0.033	112.	-0.563	732.	123.25	12.02	50.10	55.66	71.99	79.99	108.36	120.40	.474E 05	7
FLOW 6	-0.315	2310.	-0.035	1373.	-0.136	3305.	60.68	12.94	25.55	25.55	30.35	30.35	26.08	26.08	.721E 06	2
FLOW 6	-0.267	3480.	-0.029	1823.	-0.135	4977.	51.36	10.57	22.08	22.08	28.39	28.39	25.99	25.99	.876E 06	1
FLOW 7	-0.270	1168.	-0.062	1358.	-0.150	2483.	51.97	22.71	30.70	31.49	33.48	34.34	28.79	29.53	.232E 06	7
FLOW 7	-0.229	1926.	-0.059	1841.	-0.126	3656.	44.05	21.48	29.10	29.85	31.04	31.83	24.29	24.91	.340E 06	5

```
 STOP     0
#EXECUTION TERMINATED
#
```

B29963